FILE 'HCAPLUS' ENTERED AT 21:01:30 ON 22 JAN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'USPATFULL' ENTERED AT 21:01:30 ON 22 JAN 2004

=> d his

(FILE 'HOME' ENTERED AT 20:56:48 ON 22 JAN 2004)

FILE 'REGISTRY' ENTERED AT 20:57:10 ON 22 JAN 2004
L1 STRUCTURE UPLOADED
L2 1 S L1 SSS SAM
L3 9 S L1 SSS FULL

FILE 'HCAPLUS, USPATFULL' ENTERED AT 20:58:23 ON 22 JAN 2004
L4 40 S L3
L5 6 S L4 AND ARTHRIT?
L6 6 DUP REM L5 (0 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 20:59:19 ON 22 JAN 2004

FILE 'HCAPLUS, USPATFULL' ENTERED AT 21:01:30 ON 22 JAN 2004

=> s l4 not l6
L7 34 L4 NOT L6

=> s l7 and (tumor? or cancer? or metastas? or carcinom? or neoplas? or osteoarthrit? or sepsis or septic or osteoporo?)
L8 33 L7 AND (TUMOR? OR CANCER? OR METASTAS? OR CARCINOM? OR NEOPLAS? OR OSTEOARTHRIT? OR SEPSIS OR SEPTIC OR OSTEOPORO?)

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9 29 DUP REM L8 (4 DUPLICATES REMOVED)

=> d l9 abs ibib kwic hitstr 1-29

L9 ANSWER 1 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
AB Urea derivs. of formula A-NHCONH-B or pharmaceutically acceptable salts thereof [A = a substituted moiety of up to 40 carbon atoms of the formula -L-(M-L1)q; where L = a 5 or 6 membered cyclic structure bound directly to D; L1 = a substituted cyclic moiety having at least 5 members; M = a bridging group having at least one atom; q = an integer of 1-3; each cyclic structure of L and L1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur; B = a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D contg. 0-4 members of the group consisting of nitrogen, oxygen and sulfur] are prepd. These compds. are useful for raf mediated diseases, in particular a **cancerous** cell growth mediated by raf kinase. All compds. exemplified, e.g. N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea, displayed IC50 of between 1 mM and 10 .mu.M.

ACCESSION NUMBER: 2003:874965 HCAPLUS
DOCUMENT NUMBER: 139:364958
TITLE: Preparation of omega-carboxyaryl substituted diphenyl ureas as raf kinase inhibitors
INVENTOR(S): Riedl, Bernd; Dumas, Jacques; Khire, Uday; Lowinger, Timothy B.; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Monahan, Mary-Katherine; Natero, Reina; Renick, Joel; Sibley, Robert N.
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 60 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003207872	A1	20031106	US 2002-42226	20020111

PRIORITY APPLN. INFO.: US 2002-42226 20020111
OTHER SOURCE(S): MARPAT 139:364958

AB . . . group consisting of nitrogen, oxygen and sulfur] are prepd. These compds. are useful for raf mediated diseases, in particular a **cancerous** cell growth mediated by raf kinase. All compds. exemplified, e.g. N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea, displayed IC50 of between 1 mM and 10 .mu.M.

ST carboxyaryldiphenylurea prepn raf kinase inhibitor; **cancerous** cell growth treatment carboxyaryldiphenylurea prepn; raf mediated disease treatment carboxyaryldiphenylurea prepn; phenylpyridyloxyphenylurea prepn raf kinase inhibitor

IT Antitumor agents
Neoplasm
(prepn. of .omega.-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors for treating raf-mediated diseases such as **cancerous** cell growth)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(raf; prepn. of .omega.-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors for treating raf-mediated diseases such as **cancerous** cell growth)

IT 284462-67-5P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-(4-aminophenyl)urea 284462-68-6P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-(4-ethoxycarbonylphenyl)urea 284462-97-1P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-(4-carboxyphenyl)urea 604813-15-2P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[3-(5-methoxycarbonylpyridyl)oxy]phenyl]urea 620963-02-2P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-(3-methoxycarbonylphenyl)carboxyaminophenyl]urea 620963-04-4P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-(3-methylcarbamoylphenyl)carboxyaminophenyl]urea
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(intermediate; prepn. of .omega.-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors for treating raf-mediated diseases such as **cancerous** cell growth)

IT 349-65-5P, 2-Methoxy-5-(trifluoromethyl)aniline 703-12-8P, N-Methyl-4-bromobenzenesulfonamide 883-62-5P, 3-Methoxy-2-naphthoic Acid 1215-98-1P, 4-(4-Acetylphenoxy)aniline 13041-60-6P, Methyl 3-methoxy-2-naphthoate 16588-75-3P, 2-Methoxy-5-(trifluoromethyl)phenyl isocyanate 27237-21-4P, 4-(3-Carboxyphenoxy)-1-nitrobenzene 36089-89-1P, 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene 41513-02-4P, 4-Bromo-3-(trifluoromethyl)phenyl Isocyanate 50727-06-5P, 5-Hydroxyisoindoline-1,3-dione 51727-15-2P, 4-Chloropyridine-2-carbonyl chloride hydrochloride 53750-66-6P, 4-Chloropyridine-2-carbonyl chloride 54579-63-4P, 4-(3-Carboxyphenoxy)aniline 64064-63-7P, 4-(2-Methyl-5-pyridyloxy)-1-nitrobenzene 67291-63-8P, 2-Amino-3-methoxynaphthalene 71708-64-0P, 4-[3-(N-Methylcarbamoyl)phenoxy]-1-nitrobenzene 73441-73-3P, 4-[4-(N-Methylsulfamoyl)phenoxy]-1-nitrobenzene 73441-86-8P, 4-[4-(N-Methylsulfamoyl)phenyloxy]aniline 75919-92-5P, 4-(4-Acetylphenoxy)-1-nitrobenzene 77992-50-8P, 4-Bromo-3-(trifluoromethyl)aniline monohydrochloride 99586-65-9P, 4-Chloro-2-pyridinecarboxamide 114780-06-2P, 4-Chloro-N,N-dimethyl-2-pyridinecarboxamide 119431-22-0P, 3-Chloro-4-(2,2,2-trifluoroacetylamino)phenol 153435-79-1P, N-Methyl-3-bromobenzenesulfonamide 176977-85-8P, Methyl 4-chloropyridine-2-carboxylate hydrochloride 220000-87-3P, 4-Chloro-N-methyl-2-pyridinecarboxamide 228401-15-8P, 2-[N-(Carbobenzyloxy)amino]-3-methoxynaphthalene 228401-43-2P, 4-(3-Methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene 228401-44-3P, 4-(3-Carboxy-4-methoxyphenoxy)-1-nitrobenzene 284461-86-5P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-(methoxycarbonyl)-5-pyridyloxy]phenyl]urea 284462-06-2P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[[2-[N-(2-triisopropylsilyloxyethyl)carbamoyl]-4-pyridyl]oxy]phenyl]urea 284462-37-9P, 4-[2-(N-Methylcarbamyl)-4-pyridyloxy]aniline 284462-38-0P, 5-(4-Nitrophenoxy)isoindoline-1,3-dione 284462-39-1P, 5-(4-Aminophenoxy)isoindoline-1,3-dione 284462-40-4P, 1-(4-tert-Butyl-2-nitrophenyl)-2,5-dimethylpyrrole 284462-41-5P, 5-tert-Butyl-2-(2,5-dimethylpyrrolyl)aniline 284462-42-6P, 4-[2-(N-Methylcarbamoyl)-4-pyridyloxy]-2-methylaniline hydrochloride 284462-43-7P 284462-44-8P, 4-[2-(N-Methylcarbamoyl)-4-pyridyloxy]-2-chloroaniline 284462-45-9P, 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline 284462-46-0P, 4-[3-(N-Methylcarbamoyl)-4-methoxyphenoxy]-1-nitrobenzene 284462-47-1P, 4-[3-(N-Methylcarbamoyl)-4-methoxyphenoxy]aniline 284462-48-2P, 5-(4-Nitrophenoxy)-2-methylisoindoline-1,3-dione 284462-49-3P, 5-(4-Aminophenoxy)-2-methylisoindoline-1,3-dione 284462-51-7P, 4-Chloro-2-[N-(2-morpholin-4-ylethyl)carbamoyl]pyridine 284462-52-8P, 4-[2-[N-(2-Morpholin-4-ylethyl)carbamoyl]-4-pyridyloxy]aniline 284462-53-9P, 4-(1-Oxoisoindolin-5-yloxy)-1-nitrobenzene 284462-54-0P, 4-(1-Oxoisoindolin-5-yloxy)aniline 284462-55-1P, 4-(3-Ethoxycarbonylphenoxy)-1-nitrobenzene 284462-56-2P, 4-[3-(N-Methylcarbamoyl)phenoxy]aniline 284462-57-3P, 4-(5-Methoxycarbonyl-3-pyridyloxy)-1-nitrobenzene 284462-58-4P, 4-(5-Methoxycarbonyl-3-pyridyloxy)aniline 284462-59-5P, 4-[3-(N-Methylsulfamoyl)phenyloxy]benzene 284462-60-8P, 4-[3-(N-Methylsulfamoyl)phenyloxy]-1-nitrobenzene 284462-61-9P, 4-(3-Methylsulfamoylphenoxy)aniline 284462-62-0P, 4-[4-[1-(Methoxyimino)ethyl]phenoxy]aniline hydrochloride 284462-63-1P, 4-Chloro-N-(2-triisopropylsilyloxy)ethylpyridine-2-carboxamide 284462-64-2P, 4-[[2-[N-(2-Triisopropylsilyloxyethyl)carbamoyl]-4-pyridyl]oxy]aniline 284462-65-3P, 4-(2-Methoxycarbonyl-5-pyridyloxy)-1-nitrobenzene 284462-66-4P, 4-(2-Methoxycarbonyl-5-pyridyloxy)aniline

284462-74-4P, 4-[2-(N-Methylcarbamoyl)-4-pyridyloxy]-2-methylaniline
284462-77-7P, 5-tert-Butyl-2-methoxyphenyl isocyanate 284462-78-8P,
3-[-2-(N-Methylcarbamoyl)-4-pyridyloxy]aniline 284462-79-9P,
3-(2-Carbamoyl-4-pyridyloxy)aniline 284462-80-2P, 4-(2-Carbamoyl-4-
pyridyloxy)aniline 284462-82-4P, 4-[2-(N-Ethylcarbamoyl)-4-
pyridyloxy]aniline 284462-83-5P, 4-[2-(N-Methylcarbamoyl)-4-pyridyloxy]-
3-chloroaniline 284462-84-6P 284462-85-7P, 4-(3-
Carbamoylphenoxy)aniline 284462-86-8P, 4-[2-(N,N-Dimethylcarbamoyl)-4-
pyridyloxy]aniline 284462-89-1P, 4-[2-(N-Isopropylcarbamoyl)-4-
pyridyloxy]aniline 284462-92-6P, 3-[2-(N-Methylcarbamoyl)-4-pyridyloxy]-
4-methylaniline 284462-93-7P, 4-[3-[N-(2-Morpholinylethyl)carbamoyl]phen
oxy]aniline 284462-94-8P, 4-[3-[N-(2-Piperidylethyl)carbamoyl]phenoxy]an
iline 284462-95-9P, 4-[3-[N-(Tetrahydrofurylmethyl)carbamoyl]phenoxy]ani
line 284462-99-3P, 4-Chloro-2-methoxy-5-(trifluoromethyl)phenyl
isocyanate 284670-99-1P, 4-(4-Acetylphenoxy)-5-aminopyridine
284671-00-7P, N-[5-(Trifluoromethyl)-2-methoxyphenyl]-N'-[4-[3-(5-
methoxycarbonylpyridyl)oxy]phenyl]urea 284671-01-8P,
N-[5-(Trifluoromethyl)-2-methoxyphenyl]-N'-(3-carboxyphenyl)urea
573673-51-5P, 4-[4-[2-(N-Methylcarbamoyl)phenyl]thio]aniline
573673-52-6P, 3-[4-[2-(N-Methylcarbamoyl)phenyl]thio]aniline
573673-55-9P, 4-[3-[N-[(1-Methyl-2-pyrrolidinyl)methyl]carbamoyl]phenoxy]a
niline 604813-03-8P, 4-(5-Methylcarbamoyl-3-pyridyloxy)aniline
604813-05-0P 604813-07-2P, 4-Chloro-N-ethyl-2-pyridinecarboxamide
604813-08-3P, 4-Chloro-N-isopropyl-2-pyridinecarboxamide 604813-09-4P,
4-[4-(N-Methylsulfamoyl)phenoxy]benzene 604813-11-8P,
4-[3-[N-(2-Morpholinylethyl)carbamoyl]phenoxy]-1-nitrobenzene
604813-12-9P, 4-[3-[N-(2-Piperidylethyl)carbamoyl]phenoxy]-1-nitrobenzene
604813-13-0P, 4-[3-[N-(Tetrahydrofurylmethyl)carbamoyl]phenoxy]-1-
nitrobenzene 604813-14-1P, 4-[3-[N-[(1-Methyl-2-
pyrrolidinyl)methyl]carbamoyl]phenoxy]-1-nitrobenzene
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(intermediate; prepn. of .omega.-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors for treating raf-mediated diseases such as **cancerous** cell growth)

IT 139691-76-2, Raf Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of .omega.-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors for treating raf-mediated diseases such as **cancerous** cell growth)

IT 228418-48-2P 284461-33-2P 284461-34-3P 284461-35-4P 284461-36-5P
284461-37-6P 284461-38-7P 284461-39-8P 284461-40-1P 284461-41-2P
284461-42-3P 284461-43-4P 284461-44-5P 284461-45-6P 284461-46-7P
284461-47-8P 284461-48-9P 284461-49-0P 284461-50-3P 284461-51-4P
284461-52-5P 284461-53-6P 284461-54-7P 284461-55-8P 284461-56-9P
284461-57-0P 284461-58-1P 284461-59-2P 284461-60-5P 284461-61-6P
284461-62-7P 284461-63-8P 284461-64-9P 284461-65-0P 284461-66-1P
284461-67-2P 284461-68-3P 284461-70-7P 284461-71-8P 284461-72-9P
284461-73-0P 284461-74-1P 284461-75-2P 284461-76-3P
284461-77-4P **284461-78-5P** 284461-79-6P **284461-80-9P**
284461-81-0P 284461-82-1P **284461-83-2P** 284461-84-3P
284461-85-4P 284461-88-7P 284461-89-8P 284461-90-1P 284461-91-2P
284461-92-3P 284461-93-4P 284461-94-5P 284461-95-6P 284461-96-7P
284461-97-8P 284461-99-0P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-
(3-methylcarbamoylphenyl)carbamoylphenyl]urea 284462-00-6P
284462-01-7P 284462-02-8P 284462-03-9P 284462-04-0P 284462-05-1P
284462-07-3P 284462-08-4P 284462-09-5P 284462-10-8P 284462-11-9P

284462-12-0P 284462-13-1P 284462-15-3P 284462-16-4P 284462-17-5P
284462-18-6P 284462-19-7P 284462-20-0P 284462-21-1P 284462-22-2P
284462-23-3P 284462-24-4P 284462-25-5P 284462-26-6P 284462-27-7P
284462-28-8P 284462-29-9P 284462-30-2P
284462-31-3P 284462-34-6P 284462-35-7P, N-[5-(tert-Butyl)-2-(2,5-dimethylpyrrolyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea 284462-36-8P 284462-70-0P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[N-[3-[N-(3-pyridyl)carbamoyl]phenyl]carbamoyl]phenyl]urea 284670-98-0P, N,N'-Bis[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea 447457-08-1P 573673-43-5P 604813-02-7P
604813-04-9P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[[3-[5-(2-dimethylaminoethyl)carbamoyl]pyridyl]oxy]phenyl]urea 620962-97-2P
620962-98-3P 620962-99-4P 620963-00-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of .omega.-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors for treating raf-mediated diseases such as **cancerous** cell growth)

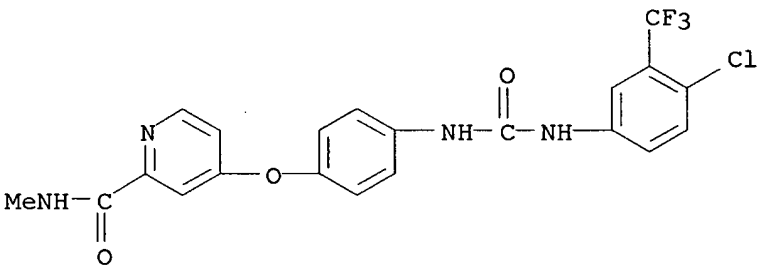
IT 474642-51-8P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-(3-carboxyphenyl)urea 573673-47-9P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[3-(5-carboxypyridyl)oxy]phenyl]urea
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(reactant; prepn. of .omega.-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors for treating raf-mediated diseases such as **cancerous** cell growth)

IT 74-88-4, Iodomethane, reactions 74-89-5, Methylamine, reactions 75-04-7, Ethylamine, reactions 75-31-0, Isopropylamine, reactions 75-44-5, Phosgene 77-78-1, Dimethyl sulfate 98-58-8, 4-Bromobenzenesulfonyl chloride 98-98-6, Picolinic acid 99-93-4, p-Hydroxyacetophenone 99-98-9, 4-(Dimethylamino)aniline 100-51-6, Benzyl alcohol, reactions 106-50-3, p-Phenylenediamine, reactions 108-00-9, N,N-Dimethylethylenediamine 108-95-2, Phenol, reactions 109-85-3, 2-Methoxyethylamine 110-13-4, Acetonylacetone 123-30-8, 4-Aminophenol 123-39-7, N-Methylformamide 124-40-3, Dimethylamine, reactions 127-19-5, Dimethylacetamide 141-43-5, 2-Hydroxyethylamine, reactions 320-51-4, 4-Chloro-3-(trifluoromethyl)aniline 327-78-6, 4-Chloro-3-(trifluoromethyl)phenyl isocyanate 350-46-9, 1-Fluoro-4-nitrobenzene 371-40-4, 4-Fluoroaniline 393-36-2, 4-Bromo-3-(trifluoromethyl)aniline 407-25-0, Trifluoroacetic anhydride 462-08-8, 3-Aminopyridine 490-79-9, 2,5-Dihydroxybenzoic acid 503-38-8, Trichloromethyl chloroformate 530-62-1, N,N'-Carbonyldiimidazole 591-27-5, 3-Aminophenol 593-56-6, O-Methylhydroxylamine hydrochloride 610-35-5, 4-Hydroxyphthalic acid 619-08-9, 2-Chloro-4-nitrophenol 626-61-9, 4-Chloropyridine 883-99-8, Methyl 3-hydroxy-2-naphthoate 1121-78-4, 5-Hydroxy-2-methylpyridine 1193-02-8, 4-Aminothiophenol 1664-40-0, N-Phenylethylenediamine 1877-71-0, Monomethyl isophthalate 2038-03-1, 4-(2-Aminoethyl)morpholine 2252-63-3, N-(4-Fluorophenyl)piperazine 2524-67-6, 4-Morpholinoaniline 2835-99-6, 4-Amino-3-methylphenol 2905-24-0, 3-Bromobenzenesulfonyl chloride 3535-88-4, 5-tert-Butyl-2-methoxyaniline 3964-52-1, 4-Amino-2-chlorophenol 4548-45-2, 2-Chloro-5-nitropyridine 4795-29-3, Tetrahydrofurfurylamine 5369-19-7, 3-tert-Butylaniline 6310-19-6, 2-Nitro-4-tert-butylaniline 6628-77-9, 5-Amino-2-methoxypyridine 6927-86-2, 4-(4-Acetylphenoxy)aniline hydrochloride 7664-41-7, Ammonia,

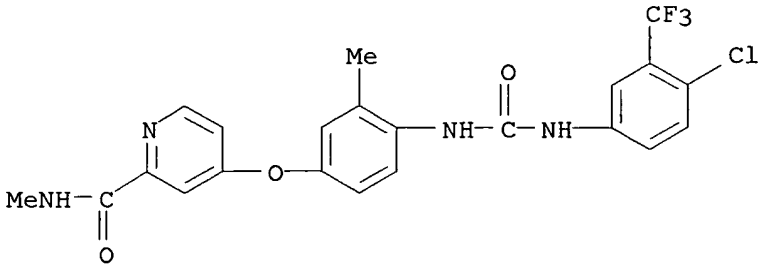
reactions 7781-98-8, Ethyl 3-hydroxybenzoate 13154-24-0, Triisopropylsilyl chloride 22948-02-3, 3-Aminothiophenol 24484-93-3, Methyl 4-chloropyridine-2-carboxylate 25900-61-2, 3-Methylcarbamoylaniline 26116-12-1, 2-Aminomethyl-1-ethylpyrrolidine 27578-60-5, 1-(2-Aminoethyl)piperidine 29264-35-5, 4-(3-Carboxy-4-hydroxyphenoxy)-1-nitrobenzene 30766-22-4, Methyl 5-hydroxynicotinate 30806-83-8, Ethyl 4-isocyanatobenzoate 32315-10-9, Bis(trichloromethyl) carbonate 34803-66-2, N-(2-Pyridyl)piperazine 36265-31-3, 4-(4-Methylthiophenoxy)-1-nitrobenzene 51639-48-6, N-(4-Acetylphenyl)piperazine 106164-64-1, 4-(3-Carbamoylphenoxy)-1-nitrobenzene 150009-83-9, 3-Amino-2-methoxyquinoline 252061-66-8, 5-Hydroxyisoindolin-1-one 284462-72-2, 3-Chloro-6-acetamido-4-(trifluoromethyl)anisole 284462-73-3, 4-Chloro-N-(2-hydroxyethyl)pyridine-2-carboxamide 447457-10-5, 4-Chloro-3-(trifluoromethyl)-2-methoxyphenyl isocyanate 604813-06-1, 4,5-Amino-2-methylphenol 620963-05-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; prepn. of .omega.-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors for treating raf-mediated diseases such as **cancerous** cell growth)

IT **284461-73-0P 284461-78-5P 284461-80-9P 284461-83-2P 284462-28-8P 284462-29-9P 284462-30-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of .omega.-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors for treating raf-mediated diseases such as **cancerous** cell growth)

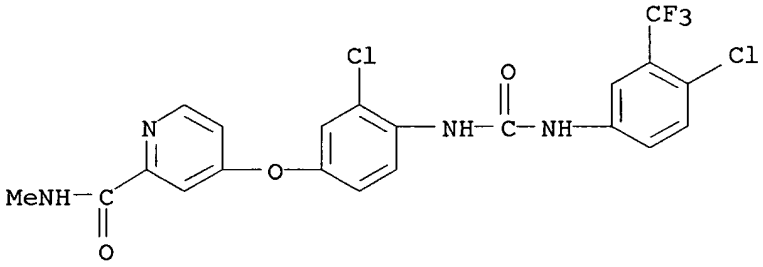
RN 284461-73-0 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



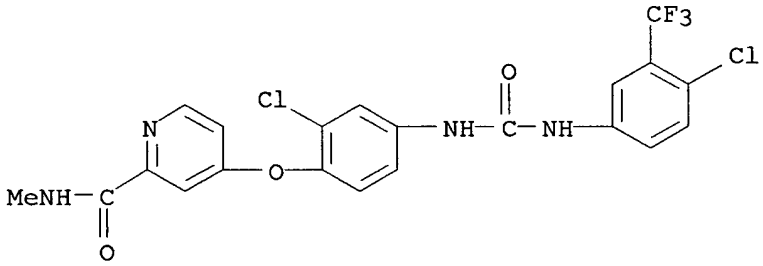
RN 284461-78-5 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-methylphenoxy]-N-methyl- (9CI) (CA INDEX NAME)



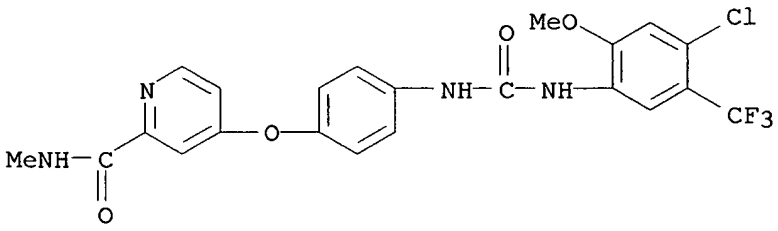
RN 284461-80-9 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



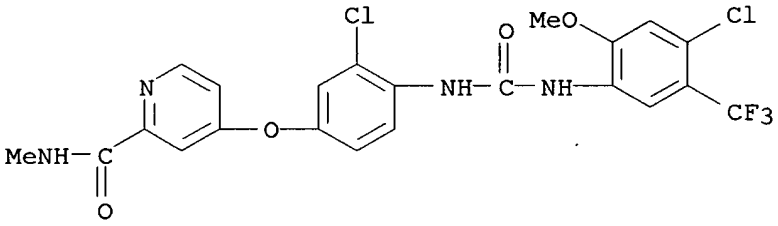
RN 284461-83-2 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



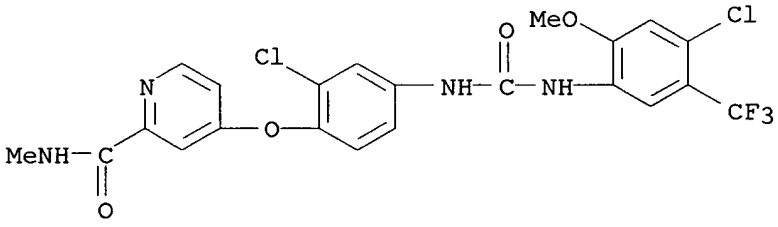
RN 284462-28-8 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-29-9 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
AB Aryl ureas of formula A-NHCONH-B [A = a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L1)q (where L = a 5 or 6 membered cyclic structure bound directly to D, L1 comprises a substituted cyclic moiety having at least 5 members; M = a bridging group having at least one atom; q = an integer of from 1-3; each cyclic structure of L and L1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur); B = a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D contg. 0-4 members of the group consisting of nitrogen, oxygen and sulfur] are prepd. These urea derivs. are useful for treating raf mediated diseases, in particular **cancerous** cell growth mediated by raf kinase. Thus, N-[4-bromo-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-

pyridyloxy]phenyl]urea. Thus, a soln. of 4-bromo-3-(trifluoromethyl)phenyl isocyanate (8.0 g, 30.1 mmol) in CH2Cl2 (80 mL) was added dropwise to a soln. of 4-[2-(N-methylcarbamoyl)-4-pyridyloxy]aniline (7.0 g, 28.8 mmol) in CH2Cl2 (40 mL) at 0.degree., stirred at room temp. for 16 h, and filtered to give, after washing the yellow solids, washing with CH2Cl2 (2 .times. 50 mL), and drying under reduced pressure (approx. 1 mmHg) at 40.degree. to give N-[4-bromo-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea. All compds. exemplified showed IC50 between 1 nM to 10 .mu.M against raf kinase.

ACCESSION NUMBER: 2003:757329 HCAPLUS
DOCUMENT NUMBER: 139:276918
TITLE: Preparation of omega-carboxyaryl substituted diphenyl ureas as raf kinase inhibitors
INVENTOR(S): Riedl, Bernd; Dumas, Jacques; Khire, Uday; Lowinger, Timothy B.; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Monahan, Mary-katherine; Natero, Reina; Renick, Joel; Sibley, Robert N.
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 61 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003181442	A1	20030925	US 2001-993647	20011127

PRIORITY APPLN. INFO.: US 2001-993647 20011127
OTHER SOURCE(S): MARPAT 139:276918

AB . . . consisting of nitrogen, oxygen and sulfur] are prepd. These urea derivs. are useful for treating raf mediated diseases, in particular **cancerous** cell growth mediated by raf kinase. Thus, N-[4-bromo-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea. Thus, a soln. of 4-bromo-3-(trifluoromethyl)phenyl isocyanate (8.0 g, 30.1 mmol) in CH2Cl2. . .

IT Antitumor agents
Neoplasm
(prepn. of omega-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors and anticancer agents)

IT 228418-48-2P 284461-33-2P, N-(3-tert-Butylphenyl)-N'-[4-[3-(methylcarbamoyl)phenoxy]phenyl]urea 284461-34-3P, N-(3-tert-Butylphenyl)-N'-[4-(4-acetylphenoxy)phenyl]urea 284461-35-4P 284461-36-5P, N-(5-tert-Butyl-2-methoxyphenyl)-N'-[4-[3-(methylcarbamoyl)phenoxy]phenyl]urea 284461-37-6P 284461-38-7P 284461-39-8P 284461-40-1P 284461-41-2P 284461-42-3P 284461-43-4P, N-(2-Methoxy-5-trifluoromethylphenyl)-N'-[3-(2-carbamoyl-4-pyridyloxy)phenyl]urea 284461-44-5P, N-(2-Methoxy-5-trifluoromethylphenyl)-N'-[4-[[2-(methylcarbamoyl)-4-pyridyl]oxy]phenyl]urea 284461-45-6P, N-(2-Methoxy-5-trifluoromethylphenyl)-N'-[4-[(2-carbamoyl-4-pyridyl)oxy]phenyl]urea 284461-46-7P 284461-47-8P 284461-48-9P 284461-49-0P, N-(2-Methoxy-5-trifluoromethylphenyl)-N'-[3-[(2-carbamoyl-4-pyridyl)oxy]-4-methylphenyl]urea 284461-50-3P 284461-51-4P 284461-52-5P 284461-53-6P 284461-54-7P 284461-55-8P 284461-56-9P 284461-57-0P, N-(2-Methoxy-5-trifluoromethylphenyl)-N'-[4-[4-[1-

(methoxyimino)ethyl]phenoxy]phenyl]urea 284461-58-1P 284461-59-2P 284461-60-5P, N-(2-Methoxy-5-trifluoromethylphenyl)-N'-[3-[[2-(methylcarbamoyl)-4-pyridyl]thio]phenyl]urea 284461-61-6P 284461-62-7P 284461-63-8P 284461-64-9P 284461-65-0P 284461-66-1P 284461-67-2P 284461-68-3P 284461-69-4P 284461-70-7P 284461-71-8P 284461-72-9P **284461-73-0P** 284461-74-1P, N-(4-Chloro-3-trifluoromethylphenyl)-N'-[4-[(2-carbamoyl-4-pyridyl)oxy]phenyl]urea 284461-75-2P, N-(4-Chloro-3-trifluoromethylphenyl)-N'-[3-[(2-carbamoyl-4-pyridyl)oxy]phenyl]urea 284461-76-3P, N-(4-Chloro-3-trifluoromethylphenyl)-N'-[3-[(2-methylcarbamoyl-4-pyridyl)oxy]phenyl]urea 284461-77-4P **284461-78-5P** 284461-79-6P **284461-80-9P** 284461-81-0P 284461-82-1P **284461-83-2P** 284461-84-3P 284461-85-4P 284461-88-7P 284461-89-8P 284461-90-1P 284461-91-2P 284461-92-3P 284461-93-4P 284461-94-5P 284461-95-6P 284461-96-7P 284461-97-8P 284462-00-6P 284462-01-7P 284462-02-8P 284462-03-9P 284462-04-0P 284462-05-1P 284462-07-3P 284462-08-4P 284462-09-5P 284462-10-8P 284462-11-9P 284462-12-0P 284462-13-1P 284462-15-3P 284462-16-4P 284462-17-5P 284462-18-6P 284462-19-7P 284462-20-0P 284462-21-1P 284462-22-2P 284462-23-3P 284462-24-4P 284462-25-5P 284462-26-6P 284462-27-7P **284462-28-8P** **284462-29-9P** **284462-30-2P** 284462-31-3P 284462-32-4P 284462-34-6P 284462-35-7P, N-[2-(2,5-Dimethyl-1-pyrrolyl)-5-tert-butylphenyl]-N'-[4-[(2-methylcarbamoyl4-pyridyl)oxy]phenyl]urea 284462-36-8P 284462-70-0P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[N-[3-[N-(3-pyridyl)carbamoyl]phenyl]carbamoyl]phenyl]urea 447457-08-1P 447457-09-2P 573673-43-5P 604813-02-7P 604813-04-9P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[3-[5-[[2-(dimethylamino)ethyl]carbamoyl]pyridyl]oxy]phenyl]urea
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of omega-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors and anticancer agents)

IT **284461-73-0P** **284461-78-5P** **284461-80-9P** **284461-83-2P** **284462-28-8P** **284462-29-9P** **284462-30-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of omega-carboxyaryl substituted di-Ph ureas as raf kinase inhibitors and anticancer agents)

RN 284461-73-0 HCAPLUS

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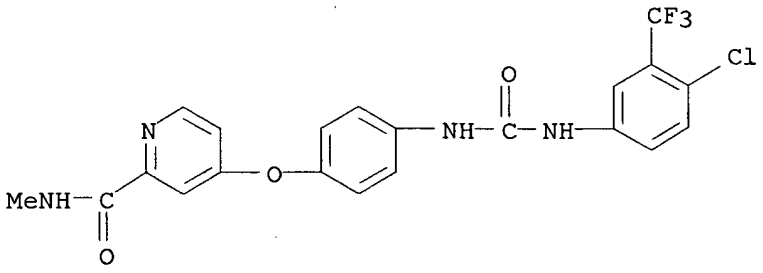
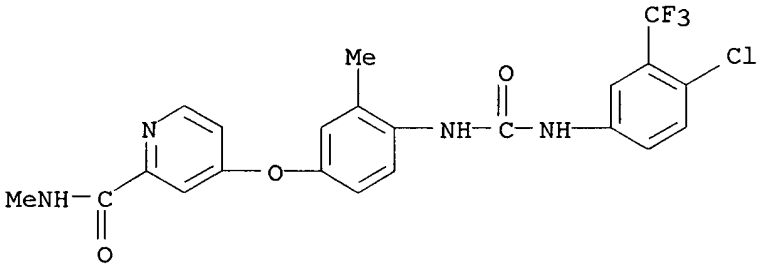
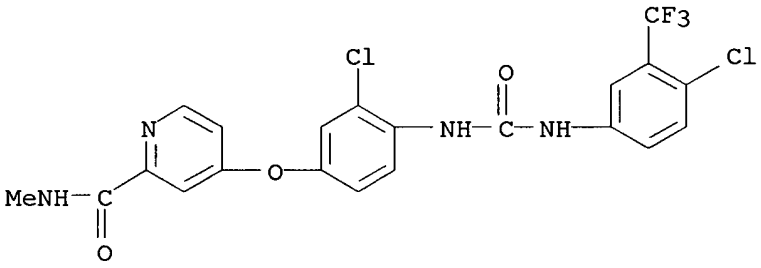


RN 284461-78-5 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-methylphenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-80-9 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-83-2 HCAPLUS
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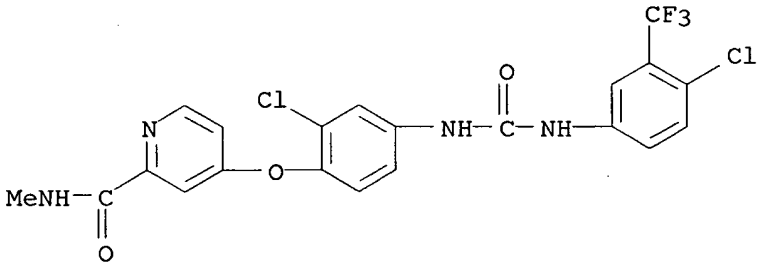
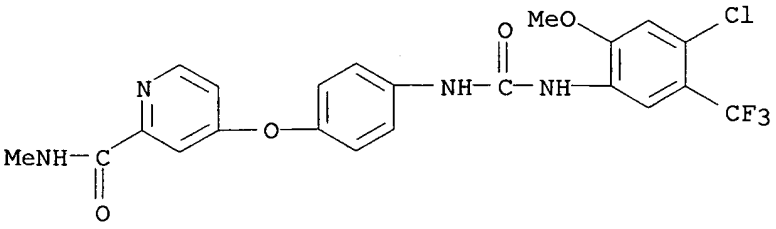
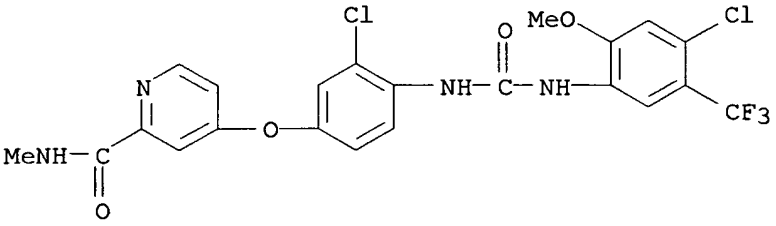


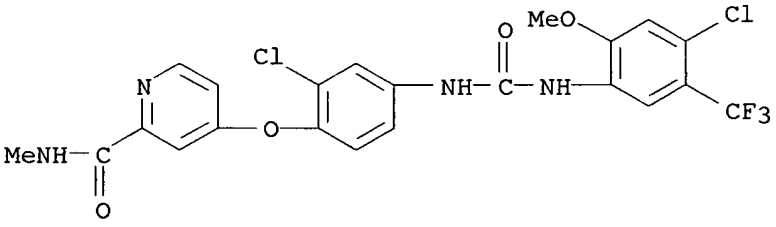
RN 284462-28-8 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-29-9 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
AB ADB [I; D = NHCONH; A = L(ML1)q; L = 5-6 membered cyclic structure bound directly to D; L1 = substituted cyclic moiety having .gtoreq.5 members, M = bridging group having .gtoreq.1 atom; q = 1-3; L, L1 contain 0-4 N, O, S; B = (substituted) up to tricyclic aryl, heteroaryl of .ltoreq.30 C atoms with .gtoreq.1 6-membered cyclic structure bound directly to D contg. 0-4 N, O, S], were prepd. Thus, 4-chloro-3-(trifluoromethyl)phenyl isocyanate in CH2Cl2 was added dropwise to a suspension of 4-[2-(N-methylcarbamoyl)-4-pyridyloxy]aniline (prepn. given) in CH2Cl2 at 0.degree.; the resulting mixt. was stirred at room temp. for 22 h. to afford N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea. I inhibited RAF kinase in the range 1 nM-1 .mu.M. I pharmaceutical compns. are claimed.
ACCESSION NUMBER: 2003:590832 HCAPLUS

DELACROIX

DOCUMENT NUMBER: 139:149528
TITLE: Preparation of diphenylureas as RAF kinase inhibitors
INVENTOR(S): Riedl, Bernd; Dumas, Jacques; Khire, Uday; Lowinger, Timothy B.; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Monahan, Mary-katherine; Natero, Reina; Renick, Joel; Sibley, Robert N.
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 62 pp., Cont. of U. S. Ser. No. 42,203.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003144278	A1	20030731	US 2002-283248	20021030
PRIORITY APPLN. INFO.:			US 2001-367380P P	20010112
			US 2002-42203 A1	20020111

OTHER SOURCE(S): MARPAT 139:149528

IT **Neoplasm**
(treatment; prepn. of diphenylureas as RAF kinase inhibitors)

IT 228418-48-2P 284461-33-2P, N-(3-tert-Butylphenyl)-N'-[4-[3-(N-methylcarbamoyl)phenoxy]phenyl urea 284461-34-3P, N-(3-tert-Butylphenyl)-N'-[4-(4-acetylphenoxy)phenyl urea 284461-35-4P 284461-36-5P, N-(5-tert-Butyl-2-methoxyphenyl)-N'-[4-[3-(N-methylcarbamoyl)phenoxy]phenyl]urea 284461-37-6P, N-(5-tert-Butyl-2-methoxyphenyl)-N'-[4-[4-methoxy-3-(N-methylcarbamoy l)phenoxy]phenyl]urea 284461-38-7P, N-(5-tert-Butyl-2-methoxyphenyl)-N'-[4-(1,3-dioxoisoindolin-5-yloxy)phenyl]urea 284461-39-8P, N-(5-tert-Butyl-2-methoxyphenyl)-N'-[4-(1-oxoisoindolin-5-yloxy)pheny l] urea 284461-40-1P 284461-41-2P 284461-42-3P, N-[2-Methoxy-5-(trifluoromethyl)phenyl]-N'-[3-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl] urea 284461-43-4P, N-[2-Methoxy-5-(trifluoromethyl)phenyl]-N'-[3-(2-carbamoyl-4-pyridyloxy) phenyl] urea 284461-44-5P, N-[2-Methoxy-5-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl] urea 284461-45-6P, N-[2-Methoxy-5-(trifluoromethyl)phenyl]-N'-[4-(2-carbamoyl-4-pyridyloxy) phenyl] urea 284461-46-7P 284461-47-8P 284461-48-9P 284461-49-0P 284461-50-3P 284461-51-4P 284461-52-5P 284461-53-6P 284461-54-7P, N-[2-Methoxy-5-(trifluoromethyl)phenyl-N'-[4-(1,3-dioxoisoindolin-5-yloxy) phenyl] Urea 284461-55-8P 284461-56-9P 284461-57-0P 284461-58-1P, N-[2-Methoxy-5-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridylthio]phenyl] urea 284461-59-2P 284461-60-5P 284461-61-6P 284461-62-7P 284461-63-8P 284461-64-9P 284461-65-0P 284461-66-1P 284461-67-2P 284461-68-3P 284461-69-4P 284461-70-7P 284461-71-8P 284461-72-9P **284461-73-0P**, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea 284461-74-1P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-(2-carbamoyl-4-pyridylox y)phenyl]urea 284461-75-2P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[3-(2-carbamoyl-4-pyridylox y)phenyl] urea 284461-76-3P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[3-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea 284461-77-4P **284461-78-5P** **284461-80-9P** 284461-81-0P 284461-82-1P **284461-83-2P** 284461-84-3P 284461-85-4P 284461-88-7P 284461-89-8P 284461-90-1P 284461-91-2P 284461-92-3P 284461-93-4P 284461-94-5P 284461-95-6P

284461-96-7P 284461-97-8P 284461-98-9P 284461-99-0P 284462-00-6P
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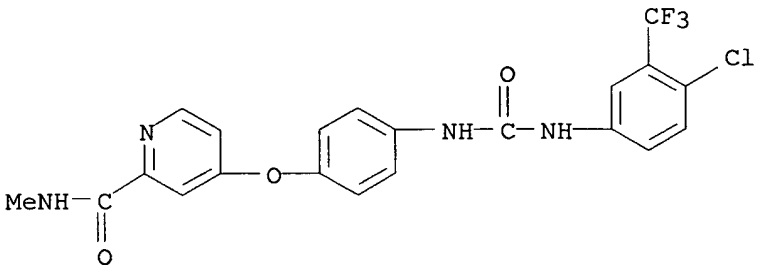
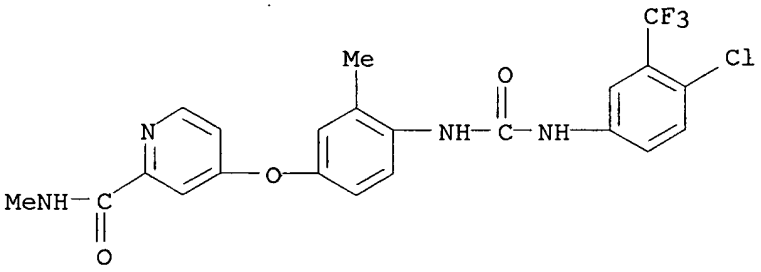
284462-26-6P 284462-27-7P **284462-28-8P**, N-[2-Methoxy-4-chloro-5-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl] urea **284462-29-9P 284462-30-2P**
284462-31-3P, N-[2-Methoxy-4-chloro-5-(trifluoromethyl)phenyl]-N'-[3-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl] urea 284462-32-4P 284462-34-6P
284462-35-7P 284462-67-5P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-(4-aminophenyl) Urea 284462-68-6P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-(4-ethoxycarbonylphenyl)urea 284462-70-0P 284462-97-1P
284670-98-0P 447457-08-1P 447457-09-2P 474642-51-8P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-(3-carboxyphenyl)urea
474642-55-2P 573673-42-4P 573673-43-5P 573673-45-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of diphenylureas as RAF kinase inhibitors)

IT **284461-73-0P**, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea **284461-78-5P 284461-80-9P 284461-83-2P 284462-28-8P**, N-[2-Methoxy-4-chloro-5-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl] urea **284462-29-9P 284462-30-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of diphenylureas as RAF kinase inhibitors)

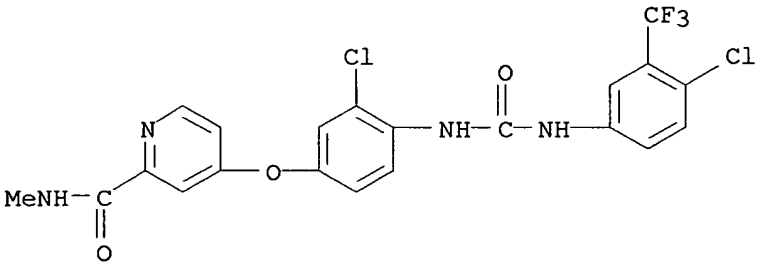
RN 284461-73-0 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



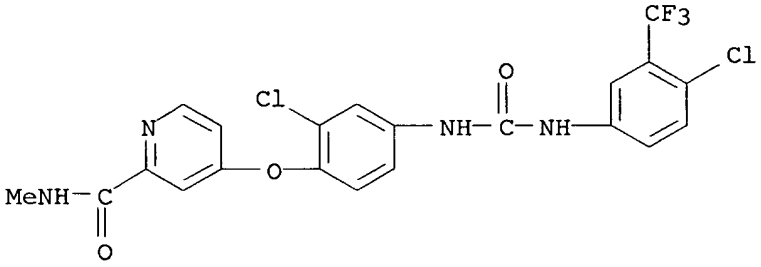
RN 284461-78-5 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-methylphenoxy]-N-methyl- (9CI) (CA INDEX NAME)



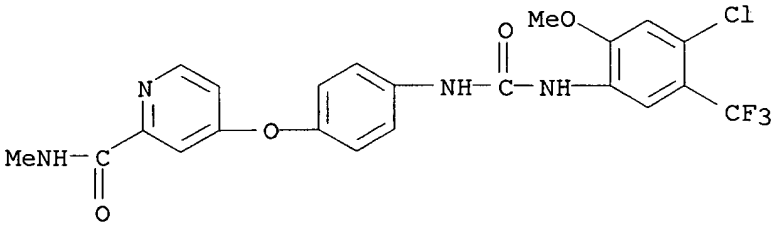
RN 284461-80-9 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



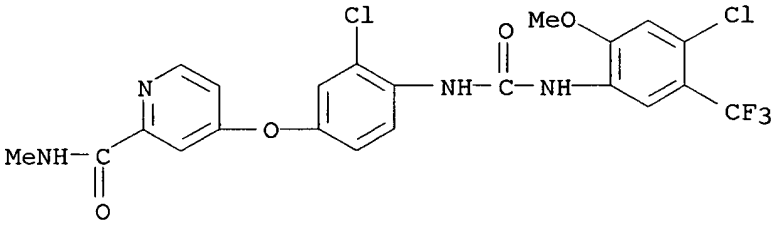
RN 284461-83-2 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



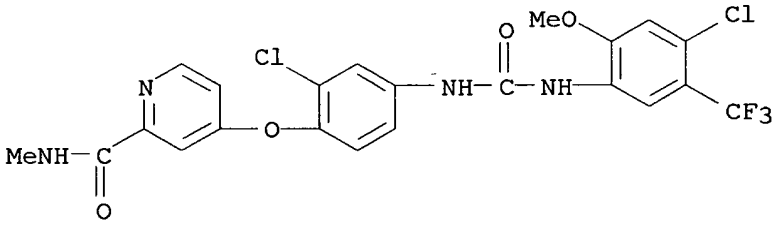
RN 284462-28-8 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-29-9 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
AB Based on drug sensitivity data and extensive gene expression data, a model was constructed by multivariate anal. with the partial least squares method type 1. Further, the model was optimized using modeling power and genetic algorithm. Thereby, the degree of contribution of the resp. genes to drug sensitivity was detd. to select genes with a high degree of contribution. In addn., the levels of gene expression in specimens were analyzed, and then the drug sensitivity was predicted based on the model. The predicted values agreed well with those drug sensitivity values detd. exptl. The drug sensitivity-predicting method provided by the present invention enables assessment of the effectiveness of a drug prior to administration using small quantities of specimens assocd. with diseases such as **cancer**. Since this enables the selection of the most suitable drug for each patient, the present invention is very useful in

improving a patient's quality of life (QOL).

ACCESSION NUMBER: 2003:737931 HCAPLUS
DOCUMENT NUMBER: 139:255332
TITLE: Method for selecting antitumor drug sensitivity-determining factors and method for predicting antitumor drug sensitivity using the selected factors
INVENTOR(S): Aoki, Yuko; Hasegawa, Kiyoshi; Ishii, Nobuya; Mori, Kazushige
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003076660	A1	20030918	WO 2002-JP2354	20020313

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2002-JP2354 20020313

AB . . . assessment of the effectiveness of a drug prior to administration using small quantities of specimens assocd. with diseases such as **cancer**. Since this enables the selection of the most suitable drug for each patient, the present invention is very useful in. . .

ST antitumor drug sensitivity gene expression DNA microarray **cancer** cell

IT Intestine, **neoplasm**
(colon; method for selecting antitumor drug sensitivity-detg. factors and predicting antitumor drug sensitivity using the selected factors)

IT Liver, **neoplasm**
(hepatoma; method for selecting antitumor drug sensitivity-detg. factors and predicting antitumor drug sensitivity using the selected factors)

IT Antitumor agents
Bladder, **neoplasm**
DNA microarray technology
Gene expression profiles, animal
Human
Lung, **neoplasm**
Mammary gland, **neoplasm**
Melanoma
Neoplasm
Ovary, **neoplasm**
PCR (polymerase chain reaction)
Pancreas, **neoplasm**
Partial least squares
Prostate gland, **neoplasm**

Test kits
(method for selecting antitumor drug sensitivity-detg. factors and predicting antitumor drug sensitivity using the selected factors)

IT Nerve, **neoplasm**
(neuroblastoma; method for selecting antitumor drug sensitivity-detg. factors and predicting antitumor drug sensitivity using the selected factors)

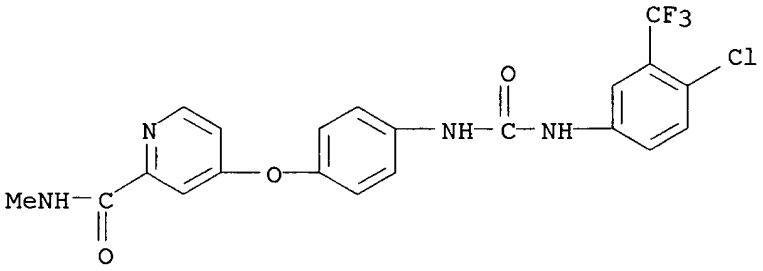
IT Lung, **neoplasm**
(non-small-cell **carcinoma**; method for selecting antitumor drug sensitivity-detg. factors and predicting antitumor drug sensitivity using the selected factors)

IT 51-21-8, 5-FU 66-22-8, 2,4(1H,3H)-Pyrimidinedione, biological studies 147-94-4, Ara-C 2207-75-2, Potassium oxonate 2353-33-5, Decitabine 3094-09-5, Furtulon 4291-63-8, Cladribine 7689-03-4, Camptothecin 10540-29-1, Tamoxifen 15663-27-1, Cisplatin 17902-23-7, Tegafur 20830-81-3, Daunomycin 25316-40-9, Adriamycin 33069-62-4, Taxol 41575-94-4, Carboplatin 53714-56-0, Leuprorelin 56420-45-2, Epirubicin 58957-92-9, Idarubicin 61422-45-5, Carmofur 75607-67-9 82640-04-8, LY156758 90357-06-5, ZD 176334 91421-42-0, 9-Nitrocamptothecin 91421-43-1, 9-Aminocamptothecin 100286-90-6, CPT-11 103766-25-2, 5-Chloro-2,4-dihydroxypyridine 105149-00-6, TZP4238 107868-30-4, FCE24304 110417-88-4, Dolastatin 10 112809-51-5, CGS 20267 114977-28-5, Taxotere 115767-74-3, TAT59 119804-96-5, DMDC 120511-73-1, ZD 1033 120685-11-2, CGP41251 123884-00-4, Dolastatin 15 123948-87-8, Topotecan 126723-15-7, Dolastatin 14 145918-75-8, Troxacitabine 149606-27-9, TZT 1027 154361-50-9, Xeloda 159776-69-9, Cemadotin 160237-25-2, BMS 184476 169869-90-3, DX-8951f 171179-06-9, PD 158780 172903-00-3, BBR 3464 182133-25-1, LY353381 182167-03-9, EM800 183319-69-9, CP 358774 184475-35-2, ZD 1839 186348-23-2, IDN 5109 189453-10-9, Epothilone D 192185-68-5, R115777 193275-84-2, SCH66336 195987-41-8, BMS 214662 204005-46-9, SU5416 212142-18-2, PTK787 212631-79-3, CI1040 219989-84-1, BMS 247550 220127-57-1, STI-571 220997-97-7, BN-80915 252916-29-3, SU6668 253863-00-2, L778123 **284461-73-0**, BAY 439006 427896-23-9, BMS 188797 437755-78-7, GW 2016 443913-73-3, ZD6474 601517-74-2, GW 2286
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for selecting antitumor drug sensitivity-detg. factors and predicting antitumor drug sensitivity using the selected factors)

IT **284461-73-0**, BAY 439006
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for selecting antitumor drug sensitivity-detg. factors and predicting antitumor drug sensitivity using the selected factors)

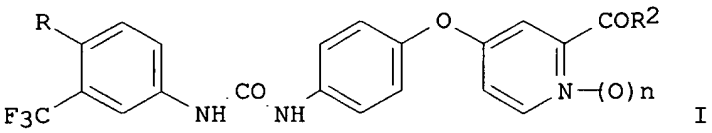
RN 284461-73-0 HCAPLUS

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
GI



I

AB Aryl ureas, such as I [R = Cl, Br; R2 = OH, NH2, NHMe, NHCH2OH, alkoxy; n = 0, 1], were prepd. for use in pharmaceutical compns. for the treatment of raf kinase and p38 kinase mediated diseases. These ureas are useful for the treatment of inflammation, **osteoporosis**, angiogenesis disorders and hyper-proliferative disorders, such as **cancer**. Thus, urea I (R = Cl, R2 = NHMe, n = 1) was prepd. with 57% yield by N-oxidn. of I (R = Cl, R2 = NHMe, n = 0) using 3-chloroperbenzoic acid in CH2Cl2 and THF. The prepd. ureas were assayed for inhibition of p38 kinase and raf kinase, as well as for **cancer** cell growth inhibition in human **cancer** cell lines, such as HCT116 and DLD-1.

ACCESSION NUMBER: 2003:656745 HCAPLUS
DOCUMENT NUMBER: 139:197377
TITLE: Preparation of aryl ureas for therapeutic use as kinase inhibitors
INVENTOR(S): Dumas, Jacques; Scott, William J.; Chien, Du-Schieng; Lee, Wendy; Bjorge, Susan; Musza, Laszlo L.; Nassar, Ala; Riedl, Bernd
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068746	A1	20030821	WO 2003-US4109	20030211

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003216446 A1 20031120 US 2003-361859 20030211
PRIORITY APPLN. INFO.: US 2002-354937P P 20020211
OTHER SOURCE(S): MARPAT 139:197377

AB . . . for the treatment of raf kinase and p38 kinase mediated diseases. These ureas are useful for the treatment of inflammation, **osteoporosis**, angiogenesis disorders and hyper-proliferative disorders, such as **cancer**. Thus, urea I (R = Cl, R2 = NHMe, n = 1) was prepd. with 57% yield by N-oxidn. of. . . CH2Cl2 and THF. The prepd. ureas were assayed for inhibition of p38 kinase and raf kinase, as well as for **cancer** cell growth inhibition in human **cancer** cell lines, such as HCT116 and DLD-1.

ST aryl urea prepn kinase inhibitor; antitumor agent prepn aryl urea; inflammation treatment aryl urea prepn; **osteoporosis** treatment aryl urea prepn; **cancer** treatment aryl urea prepn; proliferative disorder treatment aryl urea prepn; angiogenesis inhibitor aryl urea prepn

IT Inflammation
Neoplasm
Osteoporosis
(treatment; prepn. of aryl ureas for therapeutic use as kinase inhibitors)

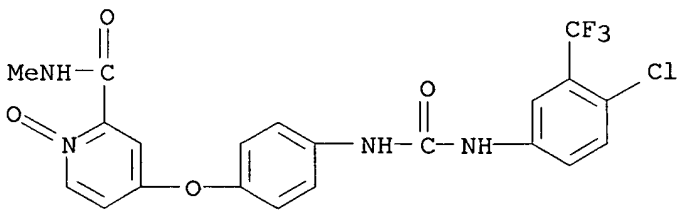
IT 284461-74-1P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-carbamoyl(4-pyridyloxy)phenyl]urea 284462-18-6P **583840-03-3P** 583840-04-4P 583840-09-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of aryl ureas for therapeutic use as kinase inhibitors)

IT 99586-65-9P, 4-Chloro-2-pyridinecarboxamide **284461-73-0P**, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)(4-pyridyloxy)phenyl]urea 284462-80-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of aryl ureas for therapeutic use as kinase inhibitors)

IT **583840-03-3P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of aryl ureas for therapeutic use as kinase inhibitors)

RN 583840-03-3 HCAPLUS

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-, 1-oxide (9CI) (CA INDEX NAME)



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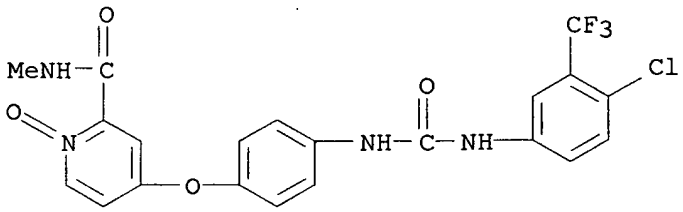
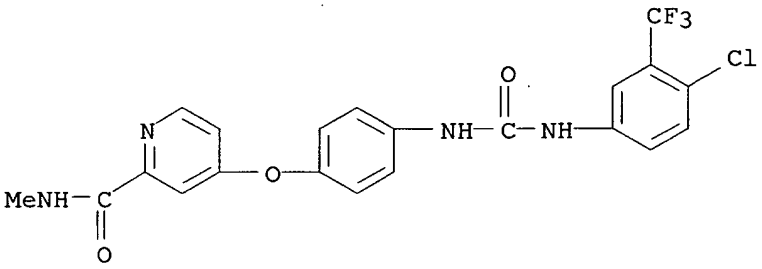


IT **284461-73-0P**, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)(4-pyridyloxy)phenyl]urea
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of aryl ureas for therapeutic use as kinase inhibitors)
RN 284461-73-0 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
AB Methods are provided for treating diseases assocd. with abnormal activity of kinases such as chronic myelogenous leukemia. The method comprises: administering a DNA methylation inhibitor to the patient in therapeutically effective amt.; and administering a kinase inhibitor such as imatinib mesylate to the patient in therapeutically effective amt., such that the in vivo activity of the kinase is reduced relative to that prior to the treatment. The method can be used to treat **cancer** assocd. with abnormal activity of kinases such as phosphatidylinositol 3'-kinase (P13K), protein kinases including serine/threonine kinases such as Raf kinases, protein kinase kinases such as MEK, and tyrosine kinases such as those in the epidermal growth factor receptor family (EGFR), platelet-derived growth factor receptor family (PDGFR), vascular endothelial growth factor receptor (VEGFR) family, nerve growth factor receptor family (NGFR), fibroblast growth factor receptor family (FGFR) insulin receptor family, ephrin receptor family, Met family, Ror family, c-kit family, Src family, Fes family, JAK family, Fak family, Btk family, Syk/ZAP-70 family, and Abl family.
ACCESSION NUMBER: 2003:633416 HCAPLUS
DOCUMENT NUMBER: 139:173786
TITLE: Method for treating diseases associated with abnormal kinase activity
INVENTOR(S): Lyons, John; Rubinfeld, Joseph
PATENT ASSIGNEE(S): Supergen, Inc., USA

SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003065995	A2	20030814	WO 2003-US3537	20030206
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003147813	A1	20030807	US 2002-71849	20020207

PRIORITY APPLN. INFO.: US 2002-71849 A1 20020207
US 2002-206854 A1 20020726

AB . . . activity of the kinase is reduced relative to that prior to the treatment. The method can be used to treat **cancer** assocd. with abnormal activity of kinases such as phosphatidylinositol 3'-kinase (P13K), protein kinases including serine/threonine kinases such as Raf kinases,. . .

IT Digestive tract, **neoplasm**
Ovary, **neoplasm**
Pancreas, **neoplasm**
(**carcinoma**; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Intestine, **neoplasm**
(colon; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT **Neoplasm**
(epithelial; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT **Neoplasm**
(**metastasis**; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Mast cell
(**neoplasm**, mastocytoma; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Neck, anatomical
(**neoplasm**, squamous cell **carcinoma**; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Hematopoietic precursor cell
Mesenchyme
Osteoblast

(**neoplasm**; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Nerve, **neoplasm**
(neuroblastoma; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Nerve, **neoplasm**
(neuroma; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Lung, **neoplasm**
(non-small-cell **carcinoma**; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Thyroid gland, **neoplasm**
(papillary **carcinoma**; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Kidney, **neoplasm**
(renal cell **carcinoma**; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT **Neoplasm**
(solid; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Head, **neoplasm**
(squamous cell **carcinoma**; treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

IT Anti-inflammatory agents
Antiasthmatics
Antitumor agents
Asthma
Autoimmune disease
Carcinoma
Drug interactions
Human
Inflammation
Leukemia
Lung, **neoplasm**
Lymphoma
Mammary gland, **neoplasm**
Multiple myeloma
Neoplasm
Prostate gland, **neoplasm**
Thyroid gland, **neoplasm**
(treatment of diseases assocd. with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

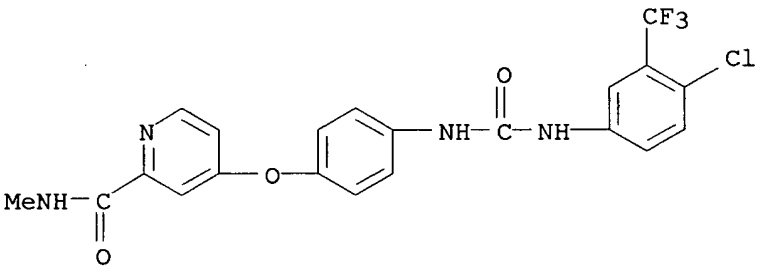
IT 109511-58-2, U0126 154447-36-6, LY294002 167869-21-8, PD98059 212631-79-3, PD184352 **284461-73-0**, BAY 43-9006
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of diseases assocd. with abnormal kinase activity with serine/threonine kinase inhibitor and DNA methylation inhibitor)

IT **284461-73-0**, BAY 43-9006
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(treatment of diseases assocd. with abnormal kinase activity with serine/threonine kinase inhibitor and DNA methylation inhibitor)

RN 284461-73-0 HCAPLUS

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The invention discloses aryl urea compds. in combination with cytotoxic or cytostatic agents for use in treating raf kinase-mediated diseases, e.g. **cancer**.

ACCESSION NUMBER: 2003:454119 HCAPLUS

DOCUMENT NUMBER: 139:17567

TITLE: Aryl urea compounds in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases

INVENTOR(S): Carter, Christopher A.; Dumas, Jacques; Gibson, Neil; Hibner, Barbara; Humphrey, Rachel W.; Trail, Pamela; Vincent, Patrick W.; Zhai, Yifan; Riedl, Bernd; Khire, Uday; Lowinger, Timothy B.; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Monahan, Mary-Katherine; Natero, Reina; Renick, Joel; Sibley, Robert N.

PATENT ASSIGNEE(S): Bayer Corporation, USA; Bayer AG

SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003047579	A1	20030612	WO 2002-US38439	20021203
WO 2003047579	B1	20030821		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003232765	A1	20031218	US 2002-308187	20021203

PRIORITY APPLN. INFO.: US 2001-334609P P 20011203
OTHER SOURCE(S): MARPAT 139:17567

TI Aryl urea compounds in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases

AB . . . invention discloses aryl urea compds. in combination with cytotoxic or cytostatic agents for use in treating raf kinase-mediated diseases, e.g. **cancer**.

ST aryl urea cytotoxic agent combination **cancer** treatment; raf kinase disease treatment aryl urea cytotoxic agent combination

IT Drug interactions
(additive; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Intercalation
(agents, DNA intercalators; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Growth factor receptors
Hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonists and antagonists; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Alkylating agents, biological
Antitumor agents
Cytotoxic agents
Drug delivery systems
Head, **neoplasm**
Human
Kidney, **neoplasm**
Leukemia
Lung, **neoplasm**
Mammary gland, **neoplasm**
Melanoma
Neoplasm
Neuroglia, **neoplasm**
Ovary, **neoplasm**
Pancreas, **neoplasm**
Prostate gland, **neoplasm**
Stomach, **neoplasm**
(aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Pancreas, **neoplasm**
(**carcinoma**; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Intestine, **neoplasm**
(colon, **carcinoma**; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Intestine, **neoplasm**
(colon; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Microtubule

(disruptors; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems
(gels, topical; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Liver, **neoplasm**
(hepatoma; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems
(infusions; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems
(inhalants; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems
(injections, i.m.; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems
(injections, i.v.; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems
(injections, s.c.; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT DNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(intercalators; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems
(liqs.; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Neck, anatomical
(**neoplasm**; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Lung, **neoplasm**
(non-small-cell **carcinoma**; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems
(oral; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems
(parenterals; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems

(sustained-release; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT Drug delivery systems
(tablets; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT 139691-76-2, Raf kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT 50-07-7, Mitomycin C 50-18-0, Cyclophosphamide 50-76-0, Actinomycin D 51-21-8, 5-Fluorouracil 57-13-6D, Urea, aryl derivs. 57-22-7, Vincristine 59-05-2, Methotrexate 147-94-4, AraC 148-82-3, Melphalan 154-93-8, BCNU 865-21-4, Vinblastine 4342-03-4, DTIC 5536-17-4, AraA 13010-47-4, CCNU 15663-27-1, Cisplatin 23214-92-8, Doxorubicin 25316-40-9, Doxorubicin hydrochloride 33069-62-4, Paclitaxel 33419-42-0, Etoposide 41575-94-4, Carboplatin 71486-22-1, Vinorelbine 95058-81-4, Gemcitabine 97682-44-5, Irinotecan 114977-28-5, Taxotere 122111-03-9, Gemzar 125317-39-7, Navelbine 180288-69-1, Herceptin 184475-35-2, Gefitinib **475207-59-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

IT 142805-56-9, DNA topoisomerase II 143180-75-0, DNA topoisomerase I
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

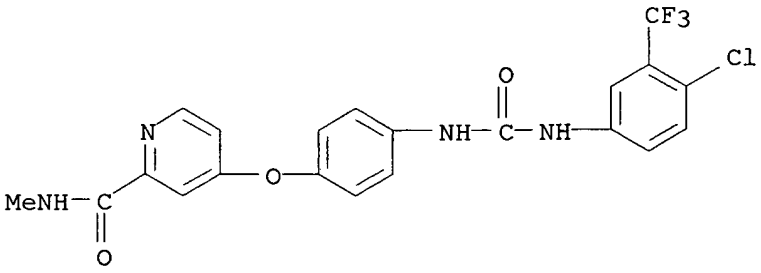
IT **475207-59-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human **cancers** and other raf kinase-mediated diseases)

RN 475207-59-1 HCAPLUS

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-, mono(4-methylbenzenesulfonate) (9CI) (CA INDEX NAME)

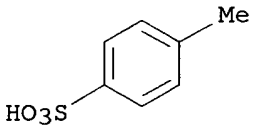
CM 1

CRN 284461-73-0
CMF C21 H16 Cl F3 N4 O3



CM 2

CRN 104-15-4
CMF C7 H8 O3 S



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

AB Materials and methods for treating certain **cancers** are described, preferably **cancers** that result from the up-regulation of the RAF-MEK-ERK pathway, and more preferably chronic myelogenous leukemia, and which **cancer** is preferably resistant to the inhibitor of Bcr-Abl tyrosine kinase, imatinib.

ACCESSION NUMBER: 2003:454071 HCAPLUS
DOCUMENT NUMBER: 139:30782
TITLE: RAF-MEK-ERK pathway inhibitors to treat **cancer**
INVENTOR(S): Lyons, John F.; Bollag, Gideon
PATENT ASSIGNEE(S): Onyx Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003047523	A2	20030612	WO 2002-US38402	20021203

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,

PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003125359 A1 20030703 US 2002-308721 20021203

PRIORITY APPLN. INFO.: US 2001-336886P P 20011204

TI RAF-MEK-ERK pathway inhibitors to treat **cancer**

AB Materials and methods for treating certain **cancers** are described, preferably **cancers** that result from the up-regulation of the RAF-MEK-ERK pathway, and more preferably chronic myelogenous leukemia, and which **cancer** is preferably resistant to the inhibitor of Bcr-Abl tyrosine kinase, imatinib.

ST RAF MEK ERK pathway inhibitor **cancer** treatment; antitumor chronic myelogenous leukemia RAF MEK ERK pathway inhibitor; imatinib resistance antitumor RAF MEK ERK pathway inhibitor

IT Antitumor agents
Drug delivery systems
Neoplasm
Signal transduction, biological
(RAF-MEK-ERK pathway inhibitors to treat **cancer**)

IT Drug resistance
(antitumor; RAF-MEK-ERK pathway inhibitors to treat **cancer**)

IT Leukemia
(chronic myelocytic; RAF-MEK-ERK pathway inhibitors to treat **cancer**)

IT Phosphorylation, biological
(protein; RAF-MEK-ERK pathway inhibitors to treat **cancer**)

IT Antitumor agents
(resistance to; RAF-MEK-ERK pathway inhibitors to treat **cancer**)

IT **284461-73-0**, BAY 43-9006
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BAY 43-9006; RAF-MEK-ERK pathway inhibitors to treat **cancer**)

IT 139691-76-2, Raf kinase 142243-02-5, ERK kinase 146702-84-3, MEK kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RAF-MEK-ERK pathway inhibitors to treat **cancer**)

IT 212631-79-3, CI 1040
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(RAF-MEK-ERK pathway inhibitors to treat **cancer**)

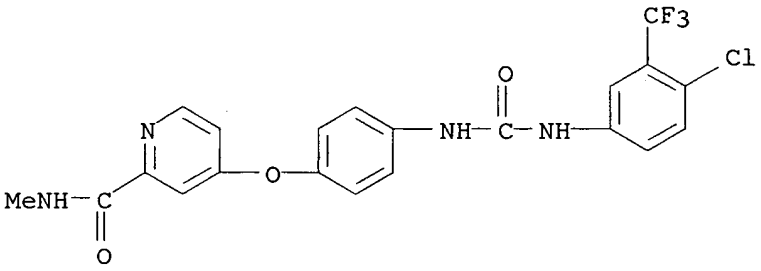
IT 138238-67-2, Bcr-abl tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, resistance to; RAF-MEK-ERK pathway inhibitors to treat **cancer**)

IT 152459-95-5, Imatinib
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(resistance to; RAF-MEK-ERK pathway inhibitors to treat **cancer**)

IT **284461-73-0**, BAY 43-9006
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BAY 43-9006; RAF-MEK-ERK pathway inhibitors to treat **cancer**)

RN 284461-73-0 HCAPLUS

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 9 OF 29 USPATFULL on STN

AB This invention relates to aryl urea compounds in combination with cytotoxic or cytostatic agents for use in treating raf kinase mediated diseases such as **cancer**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:330550 USPATFULL
TITLE:	Aryl urea compounds in combination with other cytostatic or cytotoxic agents for treating human **cancers**
INVENTOR(S):	Carter, Christopher A., Guilford, CT, UNITED STATES Gibson, Neil, East Northport, NY, UNITED STATES Hibner, Barbara, Madison, CT, UNITED STATES Humphrey, Rachel W., Woodbridge, CT, UNITED STATES Trail, Pamela, Madison, CT, UNITED STATES Vincent, Patrick W., Cheshire, CT, UNITED STATES Zhai, Yifan, Guilford, CT, UNITED STATES
PATENT ASSIGNEE(S):	BAYER CORPORATION, Pittsburgh, PA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003232765	A1	20031218	
APPLICATION INFO.:	US 2002-308187	A1	20021203	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-334609P	20011203 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS:	9
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	5 Drawing Page(s)
LINE COUNT:	1005

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Aryl urea compounds in combination with other cytostatic or cytotoxic agents for treating human **cancers**

AB . . . aryl urea compounds in combination with cytotoxic or cytostatic agents for use in treating raf kinase mediated diseases such as **cancer**.

SUMM . . . urea compounds in combination with cytotoxic or cytostatic agents and their use in treating raf kinase mediated diseases such as **cancer**.

SUMM [0003] The p21 oncogene, ras, is a major contributor to the development and progression of human solid **cancers** and is mutated in 30% of all human **cancers** (Bolton et al. Ann. Re. Med. Chem. 1994, 29, 165-174; Bos. **Cancer** Res. 1989, 49, 4682-9). In its normal, unmutated form, the ras protein is a key element of the signal transduction. . . Therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the **cancerous** growth of the cells which carry these mutants (Magnuson et al. Semin. **Cancer** Biol. 1994, 5, 247-53). It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase. . . antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human **cancer** types (Monia et al., Nat. Med. 1996, 2, 668-75).

SUMM . . . raf kinase inhibitors represent an important group of chemotherapeutic agents for use in the treatment of a variety of different **cancer** types.

SUMM . . . aryl urea compound raf kinase inhibitors which will serve to (1) yield better efficacy in reducing the growth of a **tumor** or even eliminate the **tumor** as compared to administration of either agent alone, (2) provide for the administration of lesser amounts of the administered chemotherapeutic. . . than observed with single agent chemotherapies and certain other combined therapies, (4) provide for treating a broader spectrum of different **cancer** types in mammals, especially humans, (5) provide for a higher response rate among treated patients, (6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments, (7) provide a longer time for **tumor** progression, and/or (8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other **cancer** agent combinations produce antagonistic effects.

DRWD [0006] FIG. 1 shows the response of established s.c. DLD-1 human colon **tumor** xenografts to Compound A and Camptosar alone and in combination.

DRWD [0007] FIG. 2 shows the response of established s.c. MiaPaCa-2 human pancreatic **tumor** xenografts to Compound A and Gemzar alone and in combination.

DRWD [0008] FIG. 3 shows the response of established s.c. NCI-H460 human NSCLC **tumor** xenografts to Compound A and Navelbine alone and in combination.

DRWD [0009] FIG. 4 shows the response of established MX-1 mammary **tumor** xenografts to Compound A and DOX alone and in combination.

DRWD [0010] FIG. 5 shows the response of established A549 non-small cell lung **tumor** xenografts to Compound A and Gefinitib alone and in combination.

DETD . . . below) and (b) at least one other cytotoxic or cytostatic agent in amounts which are jointly effective for treating a **cancer**, where any component (a) or (b) can also be present in the form of a pharmaceutically acceptable salt if at. . .

DETD [0036] The invention also relates to a method for treating a **cancer** that can be treated by administration of an aryl urea compound that targets raf kinase and at least one other. . . but not limited to colon, gastric, lung, pancreatic, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary **cancers**. Thus, the aryl urea compound is effective for raf kinase-mediated **cancers**. However, these compounds are also effective for **cancers** not mediated by raf kinase.

DETD [0038] In a preferred embodiment, the present invention provides methods for treating a **cancer** in a mammal, especially a human patient, comprising administering an aryl urea compound in combination with a cytotoxic or cytostatic. . .

DETD [0039] In a more preferred embodiment, the present invention provides a method for treating a **cancer** in a mammal, especially a human patient, comprising administering an aryl urea compound in combination with irinotecan.

DETD [0040] In another preferred embodiment, the present invention provides a method for treating a **cancer** in a mammal, especially a human patient, comprising administering an aryl urea compound in combination with paclitaxel.

DETD [0041] In another preferred embodiment, the present invention provides a method for treating a **cancer** in a mammal, especially a human patient, comprising administering an aryl urea compound in combination with vinorelbine.

DETD [0042] In another preferred embodiment, the present invention provides a method for treating a **cancer** in a mammal, especially a human patient, comprising administering an aryl urea compound in combination with gefinitib.

DETD [0043] In another preferred embodiment, the present invention provides a method for treating a **cancer** in a mammal, especially a human patient, comprising administering an aryl urea compound in combination with doxorubicin.

DETD [0044] In another preferred embodiment, the present invention provides a method for treating a **cancer** in a mammal, especially a human patient, comprising administering an aryl urea compound in combination with gemcitabine.

DETD [0045] In another preferred embodiment, the methods of the present invention can be used to treat a variety of human **cancers**, including but not limited to pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary **carcinomas**.

DETD . . . invention, the aryl urea compound can be administered simultaneously with a cytotoxic or cytostatic agent to a patient with a **cancer**, in the same formulation or, more typically in separate formulations and, often, using different administration routes. Administration can also be. . .

DETD [0053] Further, the invention relates to a method of inhibiting proliferation of **cancer** cells comprising contacting **cancer** cells with a pharmaceutical preparation or product of the invention, especially a method of treating a proliferative disease comprising contacting a subject, cells, tissues or a body fluid of said subject, suspected of having a **cancer** with a pharmaceutical composition or product of this invention.

DETD [0055] The term "cytotoxic" refers to an agent which can be administered to kill or eliminate a **cancer** cell. The term "cytostatic" refers to an agent which can be administered to restrain **tumor** proliferation rather than induce cytotoxic cytoreduction yielding an elimination of the **cancer** cell from the total viable cell population of the patient. The chemotherapeutic agents described herein, e.g., irinotecan, vinorelbine, gemcitabine, doxorubicin,. . . a cytostatic agent. These cytotoxic and cytostatic agents have gained wide spread use as chemotherapeutics in the treatment of various **cancer** types and are well known.

DETD . . . a theory, it is believed that by blocking this enzyme in cells, damage occurs when the cell replicates, and the **cancer** growth

is thus controlled. The cytotoxic effect is believed due to double-stranded DNA damage produced during DNA synthesis when replication. . .

DETD . . . for patients previously treated with 5-fluorouracil. Gemzar.RTM. is a pyrimidine analog that has a broad range of activity against solid **tumors** including but not limited to breast, ovarian, pancreatic, and lung **carcinomas**. It is believed to be incorporated into DNA of fast growing **cancer** cells, affecting replication. Gemzar.RTM. is a nucleoside analogue which disrupts DNA synthesis in S-phase cells and blocks the progression of. . .

DETD . . . when the receptor is stimulated by binding EGF or TGF.alpha.. Iressa is orally bioavailable and has demonstrated preclinal efficacy against **tumor** models that simultaneously express EGFR and one of its ligands, TGF.alpha.. Iressa has also been shown to inhibit the in. . .

DETD . . . intercalate in DNA and interact with DNA Topoisomerase II to induce double-stranded DNA breaks. DOX exhibits a broad spectrum of anti-**tumor** efficacy. DOX is clinically administered intravenously on an intermittent schedule. The primary route of elimination of DOX is through the. . .

DETD [0077] The invention also encompasses kits for treating mammalian **cancers**. Such kits can be used to treat a patient with a raf kinase stimulated **cancer** as well as **cancers** not stimulated through raf kinase. The kit can comprise a single pharmaceutical formulation containing an aryl urea compound and a. . . agent in separate formulations. The kit can also include instructions for how to administer the compounds to a patient with **cancer** in need of treatment. The kit can be used to treat different **cancer** types which include but are not limited to colon, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, lung, pancreatic,. . .

DETD . . . therapy of an aryl urea compound with the cytotoxic agents irinotecan, gemcitabine, vinorelbine, or paclitaxel has produced at least additive anti-**tumor** efficacy compared with that produced by administration of either the aryl urea compound or the cytotoxic agents administered alone. Generally,. . . with aryl urea compound raf kinase inhibitors will serve to (1) yield better efficacy in reducing the growth of a **tumor** or even eliminate the **tumor** as compared to administration of a single chemotherapeutic agent, (2) provide for the administration of lesser amounts of the administered. . . from larger doses of single chemotherapies and certain other combined therapies, (4) provide for treating a broader spectrum of different **cancer** types in mammals, especially humans, (5) provide for a higher response rate among treated patients, (6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments, (7) provide a longer time for **tumor** progression, and/or (8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other **cancer** agent combinations produce antagonist effects.

DETD . . . about 300 mg/kg of total body weight. Also, the agents can also be administered in conventional amounts routinely used in **cancer** chemotherapy.

DETD . . . Ncr nu/nu female mice (Taconic Farms, Germantown, N.Y.) were used for all in vivo studies invovling the DLD-1 and NCI-H460 **tumor** models. Female CB-17 SCID nice (Taconic Farms, Germantown, N.Y.) were used for studies involving the Mia-PaCa-2 **tumor**

model. The mice were housed and maintained within the Comparative Medicine Department at Bayer Corporation, West Haven, Conn. in accordance. . .

DETD [0103] **Tumor** Lines

DETD [0104] The DLD-1 human colon **carcinoma** and the MiaPaCa-2 human pancreatic **carcinoma** were obtained from the American Type Tissue Culture Collection Repository. The MX-1 human mammary **tumor** was obtained from the NCI **tumor** repository. **Tumors** were maintained as a serial in vivo passage of s.c. fragments (3.times.3 mm) implanted in the flank using a 12. . .

DETD [0105] The NCI-H460 and A549 human non-small-cell lung **carcinoma** lines were obtained from the American Type Tissue Culture Collection Repository. The NCI-H460 cells were maintained and passaged in vitro. . .

DETD [0106] **Tumor** Xenograft Experiments

DETD [0107] Female mice were implanted s.c. with DLD-1, MX-1 or Mia-PaCa-2 **tumor** fragments from an in vivo passage. Studies with the NCI-H460 and A549 cells were initiated by harvesting cells from an. . . s.c. in the right flank of each mouse. All treatment was initiated when all mice in the experiment had established **tumors** ranging in size from 100 to 150 mg. The general health of mice was monitored and mortality was recorded daily. **Tumor** dimensions and body weights were recorded twice a week starting with the first day of treatment. Animals were euthanized according. . .

DETD [0108] **Tumor** weights were calculated using the equation (l.times.w.sup.2)/2, where l and w refer to the larger and smaller dimensions collected at each measurement. In each experiment, an evaluation endpoint was selected such that the median time for the **tumors** in the control group to attain that size was slightly greater than the duration of treatment. Anti-**tumor** efficacy was measured as the incidence of complete regressions (CR) defined as **tumors** that are reduced to below the limit of measurement (3 mm) in both length and width, partial regressions (PR) defined as **tumors** that are reduced by more than 50% but less than 100% of their initial size, and percent **tumor** growth suppression (% TGS). TGS is calculated by the equation [(T-C)/C]*100, where T and C represent the times for the median **tumors** in the treated (T) and untreatred control (C) groups, respectively, to attain the evaluation size for that experiment.

DETD [0111] The most intensive combination chemotherapy anticipated in the clinical development of compound A for the treatment of **cancer** would involve daily administration of compound A administered throughout the period of time encompassing the intermittent administration of cytotoxic/cytostatic agents. . .

DETD . . . 80 mg/kg/dose. All treatment was initiated on Day 7 post-implant when all animals had small but established DLD-1 human colon **tumor** xenografts averaging 108 mg in size. Control **tumors** grew progressively in all animals with an average doubling time of 4.4 days. The evaluation endpoint used to calculate the growth delay parameters was time to three mass doublings. The median time for the **tumors** in the untreated control group to attain that size was 10.4 days.

DETD . . . weight loss and no lethality. The 40 mg/kg dose level produced a TGS of 71% with no complete or partial **tumor** regressions.

DETD . . . There was no increase in weight loss and no lethality associated with the combination of Camptosar.RTM. with compound A. The anti-**tumor** efficacy of the concurrent therapy was at least

additive producing a 229% TGS. This was associated with 3 PR's.

DETD . . . at 40 mg/kg/dose. All treatment was initiated on Day 7 post-implant when all animals had small but established MiaPaCa-human pancreatic **tumor** xenografts averaging 108 mg in size. Control **tumors** grew progressively in all animals with an average doubling time of 4.1 days. The evaluation endpoint used to calculate the growth delay parameters was time to two mass doublings. The median time for the **tumors** in the untreated control group to attain that size was 5.8 days.

DETD . . . with no weight loss and no lethality. This dose level produced a TGS of 154% with no complete or partial **tumor** regressions. Compound A was also well tolerated as a single agent producing no significant weight loss and no lethality at. . . 112%.There was no increase in weight loss and no lethality associated with the combination of Gemzar.RTM. with Compound A. The anti-**tumor** efficacy of the concurrent therapy of 120 mg/kg Gemzar and 40 mg/kg Compound A was at least additive producing a. . .

DETD . . . All treatment was initiated on Day 6 post-implant when all animals had small but established NCI-H460 human non-small cell lung **tumor** xenografts averaging 100 mg in size. Control **tumors** grew progressively in all animals with an average doubling time of 3.1 days. The evaluation endpoint used to calculate the growth delay parameters was time to three mass doublings. The median time for the **tumors** in the untreated control group to attain that size was 7.4 days. The 6.7 mg/kg dose level of Navelbine was. . .

DETD . . . q4d.times.3 schedule at 4 mg/kg/dose. All treatments were initiated on Day 6 post-implant when all animals had small but established **tumors** averaging 66 mg in size. Control **tumors** grew progressively in all animals with an average doubling time of 3.7 days. The evaluation endpoint used to calculate the growth delay parameters was time to four mass doublings. The median time for the **tumors** in the untreated control group to attain that size was 14.5 days. The 4 mg/kg dose level of DOX was. . .

DETD . . . All treatment was initiated on Day 15 post-implant when all animals had small but established A549 human non-small cell lung **tumor** xenografts averaging 110 mg in size. Control **tumors** grew progressively in all animals with an average doubling time of 10.5 days. The evaluation endpoint used to calculate the. . .

CLM What is claimed is:

5. A method for treating a **cancer** comprising administering a therapeutically effective amount of a composition comprising N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea or a pharmaceutically acceptable salt thereof and a cytotoxic. . .

7. The method of claim 5, wherein said **cancer** is mediated by raf kinase.

8. The method of claim 5, wherein said **cancer** is colon, gastric, lung, pancreatic, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, glioma, mammary, or head and neck **cancer** .

IT 50-07-7, Mitomycin C 50-18-0, Cyclophosphamide 50-76-0, Actinomycin D 51-21-8, 5-Fluorouracil 57-13-6D, Urea, aryl derivs. 57-22-7, Vincristine 59-05-2, Methotrexate 147-94-4, AraC 148-82-3, Melphalan 154-93-8, BCNU 865-21-4, Vinblastine 4342-03-4, DTIC

5536-17-4, AraA 13010-47-4, CCNU 15663-27-1, Cisplatin 23214-92-8, Doxorubicin 25316-40-9, Doxorubicin hydrochloride 33069-62-4, Paclitaxel 33419-42-0, Etoposide 41575-94-4, Carboplatin 71486-22-1, Vinorelbine 95058-81-4, Gemcitabine 97682-44-5, Irinotecan 114977-28-5, Taxotere 122111-03-9, Gemzar 125317-39-7, Navelbine 180288-69-1, Herceptin 184475-35-2, Gefitinib **475207-59-1**
(aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human cancers and other raf kinase-mediated diseases)

IT **475207-59-1**
(aryl urea compds. in combination with other cytostatic or cytotoxic agents for treating human cancers and other raf kinase-mediated diseases)

RN 475207-59-1 USPATFULL

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-, mono(4-methylbenzenesulfonate) (9CI) (CA INDEX NAME)

CM 1

CRN 284461-73-0
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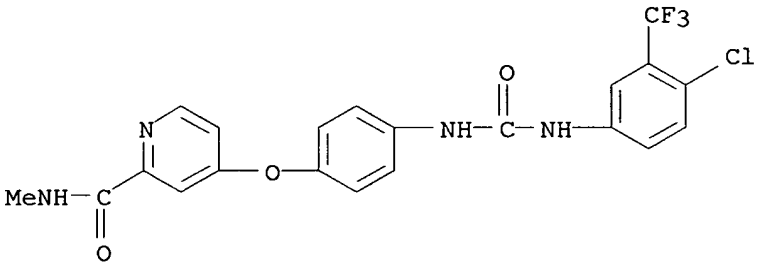

CM 2

CRN 104-15-4
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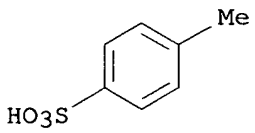

L9 ANSWER 10 OF 29 USPATFULL on STN

AB This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy of the formula

A--D--B wherein

D is --NH--C(O)--NH--

A is a substituted moiety of the formula: --L--(M--L.sup.1).sub.q, and

B is a substituted or unsubstituted up to tricyclic aryl or heteroaryl moiety with a t least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen oxygen and sulfur.

L is a 5-6 membered cyclic structure bound directly to D,

L.sup.1 comprises a substituted cyclic moiety having at least 5 members

M is a bridging group having at least one atom and q is an integer of from 1-3.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:201617 USPATFULL
TITLE:	Method and/or process for preparing omega-carboxyaryl substituted diphenyl ureas as raf kinas inhibitors
INVENTOR(S):	Riedl, Bernd, Wuppertal, GERMANY, FEDERAL REPUBLIC OF Dumas, Jacques, Bethany, CT, UNITED STATES Khire, Uday, Hamden, CT, UNITED STATES Lowinger, Timothy B., Wuppertal, GERMANY, FEDERAL REPUBLIC OF Scott, William J., Guilford, CT, UNITED STATES Smith, Roger A., Madison, CT, UNITED STATES Wood, Jill E., North Haven, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003139605	A1	20030724
APPLICATION INFO.:	US 2002-71248	A1	20020211 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-948915, filed on 10 Sep 2001, PENDING Continuation of Ser. No. US 1999-425228, filed on 22 Oct 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-257266, filed on 25 Feb 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115877P	19990113 (60)
	US 1999-115878P	19990113 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS:	25
EXEMPLARY CLAIM:	1
LINE COUNT:	3287

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0003] The p21.sup.ras oncogene is a major contributor to the development and progression of human solid **cancers** and is mutated in 30% of all human **cancers** (Bolton et al. Ann. Rep. Med. Chem. 1994, 29, 165-74; Bos. **Cancer** Res. 1989, 49, 4682-9). In its normal, unmutated form, the ras protein is a key element

of the signal transduction. . . GDP-bound resting form is strictly controlled by ras' endogenous GTPase activity and other regulatory proteins. In the ras mutants in **cancer** cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the **cancerous** growth of the cells which carry these mutants (Magnuson et al. Semin. **Cancer** Biol. 1994, 5, 247-53). It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase. . . antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human **tumor** types (Monia et al., Nat. Med. 1996, 2, 668-75).

SUMM . . . compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of **tumors** and/or **cancerous** cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal solid **cancers**, e.g., murine **cancer**, since the progression of these **cancers** is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compounds of the invention are useful in treating **cancers**, including solid **cancers**, such as, for example, **carcinomas** (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).

SUMM . . . is directed to compounds which inhibit the enzyme raf kinase and also compounds, compositions and methods for the treatment of **cancerous** cell growth mediated by raf kinase wherein a compound of Formula I is administered or pharmaceutically acceptable salt thereof.

SUMM [0056] The invention also relates to a method of treating or preventing **cancer** and other hyperproliferative disorders by administering a compound of the invention, or a pharmaceutical composition comprising one or more compounds. . .

SUMM . . . Optional anti-proliferative agents which can be added to the composition include but are not limited to compounds listed on the **cancer** chemotherapy drug regimens in the 11.sup.th Edition of the Merck Index, (1996), which is hereby incorporated by reference, such as. . .

SUMM . . . composition of the invention include but are not limited to those compounds acknowldeged to be used in the treatment of **neoplastic** diseases in Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages. . .

SUMM [0059] Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-**cancer** agents such as epothilone, irinotecan, raloxifen and topotecan.

SUMM [0060] **Cancer** and hyperproliferative disorders are defined as follows. These disorders include but are not limited to solid **tumors**, such as **cancers** of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant **metastases**. Those disorders also include lymphomas, sarcomas, and leukemias.

SUMM [0061] Examples of breast **cancer** include, but are not limited to invasive ductal **carcinoma**, invasive lobular

carcinoma, ductal **carcinoma** in situ, and lobular **carcinoma** in situ.

SUMM [0062] Examples of **cancers** of the respiratory tract include, but are not limited to small-cell and non-small-cell lung **carcinoma**, as well as bronchial adenoma and pleuropulmonary blastoma.

SUMM [0063] Examples of brain **cancers** include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal **tumor**.

SUMM [0064] **Tumors** of the male reproductive organs include, but are not limited to prostate and testicular **cancer**.

SUMM [0065] **Tumors** of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar **cancer**, as well as sarcoma of the uterus.

SUMM [0066] **Tumors** of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallblader, gastric, pancreatic, rectal, small-intestine, and salivary gland **cancers**.

SUMM [0067] **Tumors** of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral **cancers**.

SUMM [0068] Eye **cancers** include, but are not limited to intraocular melanoma and retinoblastoma.

SUMM [0069] Examples of liver **cancers** include, but are not limited to hepatocellular **carcinoma** (liver cell **carcinomas** with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct **carcinoma**), and mixed hepatocellular cholangiocarcinoma.

SUMM [0070] Skin **cancers** include, but are not limited to squamous cell **carcinoma**, Kaposi's sarcoma, malignant melanoma, Merkel cell skin **cancer**, and non-melanoma skin **cancer**.

SUMM [0071] Head-and-neck **cancers** include, but are not limited to laryngeal/hypopharyngeal/nasopharyngeal/oropharyngeal **cancer**, and lip and oral cavity **cancer**. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the. . . .

SUMM . . . with aryl urea compound raf kinase inhibitors will serve to (1) yield better efficacy in reducing the growth of a **tumor** or even eliminate the **tumor** as compared to administration of either agent alone, (2) provide for the administration of lesser amounts of the administered chemotherapeutic. . . than observed with single agent chemotherapies and certain other combined therapies, (4) provide for treating a broader spectrum of different **cancer** types in mammals, especially humans, (5) provide for a higher response rate among treated patients, (6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments, (7) provide a longer time for **tumor** progression, and/or (8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other **cancer** agent combinations produce antagonistic effects.

SUMM . . . the invention (b) at least one other cytotoxic or cytostatic agent in amounts which are jointly effective for treating a **cancer**, where any component (a) or (b) can also be present in the form of a pharmaceutically acceptable salt if at. . .

SUMM [0077] The invention also relates to a method for treating a **cancer** that can be treated by administration of a compound

according to the invention and at least one other chemotherapeutic agent. . . but not limited to colon, gastric, lung, pancreatic, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary **cancers**. Thus, the compound according to the invention is effective for raf kinase-mediated **cancers**. However, these compounds are also effective for **cancers** not mediated by raf kinase.

SUMM [0079] The present invention provides methods for treating a **cancer** in a mammal, especially a human patient, comprising administering an a compound according to the invention in combination with a. . .

SUMM [0080] In another embodiment, the methods of the present invention can be used to treat a variety of human **cancers**, including but not limited to pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary **carcinomas**.

SUMM . . . compound according to the invention can be administered simultaneously with a cytotoxic or cytostatic agent to a patient with a **cancer**, in the same formulation or, more typically in separate formulations and, often, using different administration routes. Administration can also be. . .

SUMM [0087] Further, the invention relates to a method of inhibiting proliferation of **cancer** cells comprising contacting **cancer** cells with a pharmaceutical preparation or product of the invention, especially a method of treating a proliferative disease comprising contacting a subject, cells, tissues or a body fluid of said subject, suspected of having a **cancer** with a pharmaceutical composition or product of this invention.

SUMM [0090] The term "cytotoxic" refers to an agent which can be administered to kill or eliminate a **cancer** cell. The term "cytostatic" refers to an agent which can be administered to restrain **tumor** proliferation rather than induce cytotoxic cytoreduction yielding an elimination of the **cancer** cell from the total viable cell population of the patient. The chemotherapeutic agents described herein, e.g., irinotecan, vinorelbine, gemcitabine, and. . . considered cytotoxic agents. These cytotoxic and cytostatic agents have gained wide spread use as chemotherapeutics in the treatment of various **cancer** types and are well known.

DETD [0438] For in vitro growth assay, human **tumor** cell lines, including but not limited to HCT116 and DLD-1, containing mutated K-ras genes are used in standard proliferation assays for anchorage dependent growth on plastic or anchorage independent growth in soft agar. Human **tumor** cell lines were obtained from ATCC (Rockville Md.) and maintained in RPMI with 10% heat inactivated fetal bovine serum and. . .

DETD [0442] An in vivo assay of the inhibitory effect of the compounds on **tumors** (e.g., solid **cancers**) mediated by raf kinase can be performed as follows:

DETD . . . mice are dosed i.p., i.v. or p.o. at 10, 30, 100, or 300 mg/Kg beginning on approximately day 10, when **tumor** size is between 50-100 mg. Animals are dosed for 14 consecutive days; **tumor** size is monitored with calipers twice a week.

DETD [0444] The inhibitory effect of the compounds on raf kinase and therefore on **tumors** (e.g., solid **cancers**) mediated by raf kinase can further be demonstrated in vivo according to the technique of Monia et al. (Nat. Med.. . .

CLM What is claimed is:

22. A method of treating or preventing **osteoporosis**, inflammation, and angiogenesis disorders, with the exclusion of **cancer**, in a mammal by administering an effective amount of a compound of claim 1 to said mammal.

23. A method of treating liver **cancer** in a mammal by administering an effective amount of a compound of claim 1 to said mammal.

24. A method as in claim 24, wherein the liver **cancer** is hepatocellular **carcinoma**, cholangiocarcinoma, and mixed hepatocellular cholangiocarcinoma.

IT 228418-48-2P 284461-33-2P 284461-34-3P 284461-35-4P 284461-36-5P
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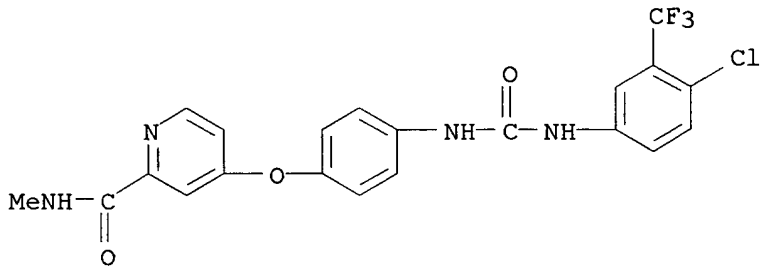
284462-36-8P 284462-70-0P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

IT **284461-73-0P 284461-78-5P 284461-80-9P**
284461-83-2P 284462-28-8P 284462-29-9P
284462-30-2P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

RN 284461-73-0 USPATFULL

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-78-5 USPATFULL
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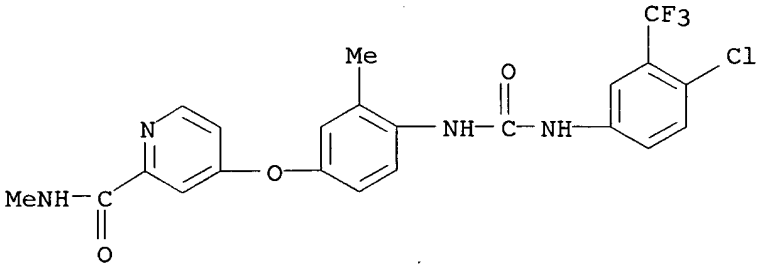

RN 284461-80-9 USPATFULL
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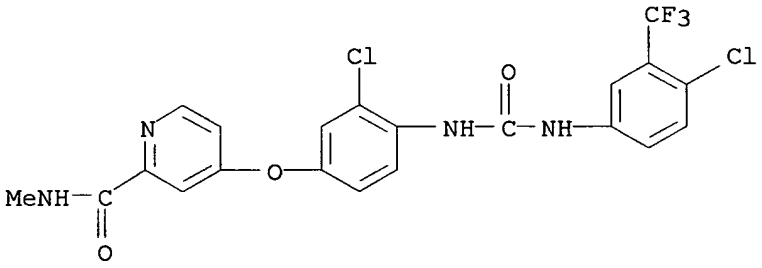

RN 284461-83-2 USPATFULL
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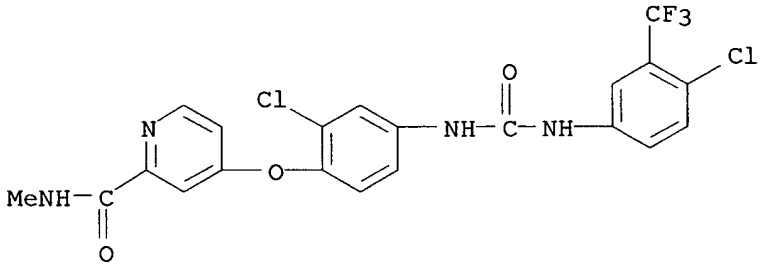

RN 284462-28-8 USPATFULL
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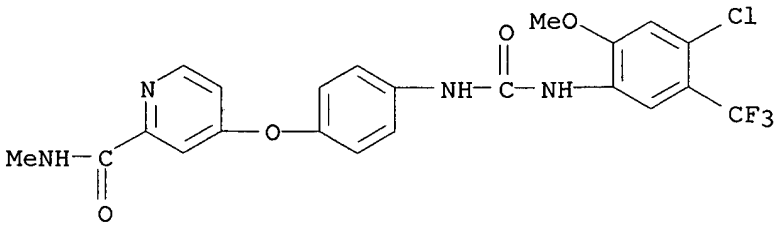
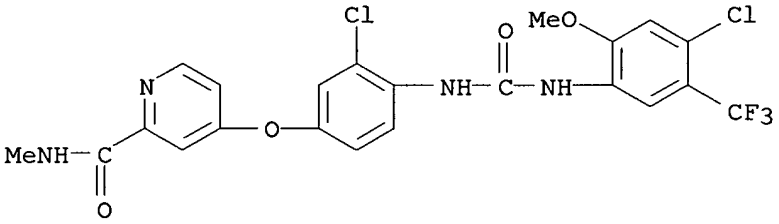
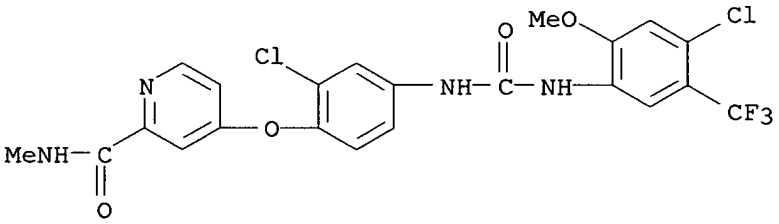


RN 284462-29-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 11 OF 29 USPATFULL on STN
AB Materials and methods for treating certain **cancers** are described, preferably **cancers** that result from the up-regulation of the RAF-MEK-ERK pathway, and more preferably chronic myelogenous leukemia, and which **cancer** is preferably resistant to the inhibition of the Bcr-Abl tyrosine kinase, imatinib.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:181526 USPATFULL
TITLE: RAF-MEK-ERK pathway inhibitors to treat **cancer**
INVENTOR(S): Lyons, John F., Moraga, CA, UNITED STATES
Bollag, Gideon, Hercules, CA, UNITED STATES

NUMBER KIND DATE

PATENT INFORMATION:	US 2003125359	A1	20030703
APPLICATION INFO.:	US 2002-308721	A1	20021203 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-336886P	20011204 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Gregory Giotta, Ph.D., Vice President and Chief Legal Counsel, ONYX Pharmaceuticals, Inc., 3031 Research Drive, Richmond, CA, 94806
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 373
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI RAF-MEK-ERK pathway inhibitors to treat **cancer**

AB Materials and methods for treating certain **cancers** are described, preferably **cancers** that result from the up-regulation of the RAF-MEK-ERK pathway, and more preferably chronic myelogenous leukemia, and which **cancer** is preferably resistant to the inhibition of the Bcr-Abl tyrosine kinase, imatinib.

SUMM [0001] The invention described herein is in the field of **cancer** therapy, and preferably for the treatment of chronic myelogenous leukemia.

SUMM [0002] A goal of modem **cancer** therapy is to identify molecules in signal transduction pathways that affect cell growth, and particularly those that cause a normal cell to become **cancerous** . One such pathway is the RAF-MEK-ERK pathway, and the up-regulation of one or more of its members is thought to be responsible for a number of **cancers**. For example, patients with chronic myelogenous leukemia, herein after referred to as CML, who are in either the chronic or. . .

SUMM [0004] The Abl kinase was chosen as a molecular target in the treatment against **cancer** since 95% of patients with CML have activation of the Abl pathway that occurs through chromosomal translocations that result in. . .

SUMM [0005] The invention described herein presents methods and compositions for treating **cancers** that involve up-regulation of one or more molecules in the pathway: RAF-MEK-ERK.

SUMM . . . is a description of inhibitors of the RAF-MEK-ERK pathway that are beneficially applied to the treatment of certain forms of **cancer**, preferably CML, and more preferably to those forms of CML that are resistant to Bcr-Abl kinase inhibitors, and most preferably. . .

DRWD [0011] FIG. 1 shows the RAF-MEK-ERK pathway that becomes up-regulated in certain **cancer** cells, including chronic myelogenous leukemia. Also shown are the compounds BAY 43-9006, and CI-1040, and the proteins in the pathway. . .

DETD [0017] Based on the pathway shown in FIG. 1, it will be appreciated that in **cancers** where Raf, MEK, or ERK are up-regulated, compounds that inhibit the activities of these molecules will have beneficial effects for treating such **cancers**. An example of one such **cancer**, also shown in FIG. 1, is chronic myelogenous leukemia. Thus, treating patients with non-toxic doses of, preferably, 200-400 mg and higher of the Raf kinase inhibitor BAY 43-9006 (Endocr. Relat.

Cancer 8, 219 [2001]) will result in remissions, or minimally stabilization of the growth of the **cancer**. Furthermore, treating patients with non-toxic doses of, preferably, 200-400 mg and higher of the MEK inhibitor PD184352 (now designated CI-1040, Oncogene 19, 6594 (2000) will also lead to remissions or **cancer** growth stabilization in these patients.

DETD . . . be used alone, or in combination. They may also be used in combination with other compounds known to affect particular **cancers** where the RAF-MEK-ERK pathway is up-regulated. For example, the drug imatinib (Gleevec.TM.) is used to treat CML patients; thus, imatinib. . .

DETD . . . with imatinib. Preference is given to a pharmaceutical composition that is suitable for administration to a human suffering from a **cancer** that is responsive to inhibition of a protein tyrosine kinase. Preferably the **cancer** is CML, and more preferably it is imatinib resistant CML which composition comprises an inhibitor, or a salt thereof where. . .

DETD . . . (obtained from Dr. Charles Sawyers, University of California at Los Angeles, and described by Shah, N., et al. (August 2002) **Cancer** Cell, vol. 2: pages 117-125). The experiment was conducted as follows. On day 1, 2.times.10.sup.6 cells were plated in a. . .

CLM What is claimed is:

1. A method for treating a patient suffering from **cancer**, wherein said patients' **cancer** exhibits up-regulation of the RAF-MEK-ERK pathway, comprising administering to said **cancer** patient an effective dose of an inhibitor of said RAF-MEK-ERK pathway.

2. A method as described in claim 1, wherein said **cancer** is CML.

3. A method as described in claim 2, wherein said CML **cancer** is resistant to an inhibitor of Bcr-Abl tyrosine kinase.

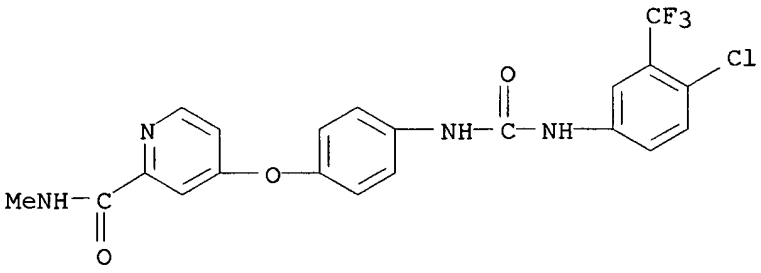
4. A method as described in claim 3, wherein said CML **cancer** is resistant to imatinib.

IT **284461-73-0**, BAY 43-9006
(BAY 43-9006; RAF-MEK-ERK pathway inhibitors to treat cancer)

IT **284461-73-0**, BAY 43-9006
(BAY 43-9006; RAF-MEK-ERK pathway inhibitors to treat cancer)

RN 284461-73-0 USPATFULL

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

AB A review. Bayer and Onyx are developing BAY-43-9006, an oral cytostatic Raf kinase inhibitor for the potential treatment of colorectal and breast **cancers**, hepatocellular **carcinoma** and non-small-cell lung **cancer**, in addn. to acute myelogenous leukemia, myelodysplastic syndrome and other **cancers**. A US IND was filed in May 2000 and by Feb. 2003 BAY-43-9006 was in phase II trials, with phase III trials expected to begin later in 2003.

ACCESSION NUMBER: 2003:736198 HCAPLUS
DOCUMENT NUMBER: 139:301125
TITLE: BAY-43-9006(Bayer/Onyx)
AUTHOR(S): Lee, John T.; McCubrey, James A.
CORPORATE SOURCE: Department of Microbiology and Immunology, Brody School of Medicine at East Carolina University, Greenville, NC, 27858-4353, USA
SOURCE: Current Opinion in Investigational Drugs (Thomson Current Drugs) (2003), 4(6), 757-763
CODEN: COIDAZ; ISSN: 1472-4472
PUBLISHER: Thomson Current Drugs
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB . . . Bayer and Onyx are developing BAY-43-9006, an oral cytostatic Raf kinase inhibitor for the potential treatment of colorectal and breast **cancers**, hepatocellular **carcinoma** and non-small-cell lung **cancer**, in addn. to acute myelogenous leukemia, myelodysplastic syndrome and other **cancers**. A US IND was filed in May 2000 and by Feb. 2003 BAY-43-9006 was in phase II trials, with phase. . .

ST review antitumor BAY439006 AML breast colorectal liver lung **cancer**

IT Cytotoxic agents
Mammary gland, **neoplasm**
Myelodysplastic syndromes
(BAY 43-9006 for treatment of **cancer** patients)

IT Antitumor agents
(acute myelogenous leukemia; BAY 43-9006 for treatment of **cancer** patients)

IT Leukemia
(acute myelogenous; BAY 43-9006 for treatment of **cancer** patients)

IT Antitumor agents
(breast **cancer**; BAY 43-9006 for treatment of **cancer** patients)

IT Antitumor agents
(colorectal **cancer**; BAY 43-9006 for treatment of **cancer** patients)

IT Intestine, **neoplasm**
(colorectal; BAY 43-9006 for treatment of **cancer** patients)

IT Liver, **neoplasm**
(hepatoma; BAY 43-9006 for treatment of **cancer** patients)

IT Antitumor agents
(liver hepatoma; BAY 43-9006 for treatment of **cancer** patients)

IT Antitumor agents
(myelodysplastic syndrome; BAY 43-9006 for treatment of **cancer** patients)

IT Lung, **neoplasm**

(non-small-cell **carcinoma**; BAY 43-9006 for treatment of **cancer** patients)

IT Antitumor agents
(non-small-cell lung **carcinoma**; BAY 43-9006 for treatment of **cancer** patients)

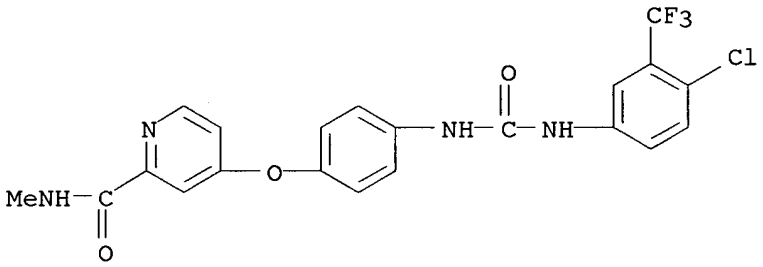
IT **284461-73-0**, BAY 43-9006
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BAY 43-9006 for treatment of **cancer** patients)

IT 139691-76-2, Raf kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; BAY 43-9006 for treatment of **cancer** patients)

IT **284461-73-0**, BAY 43-9006
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BAY 43-9006 for treatment of **cancer** patients)

RN 284461-73-0 HCAPLUS

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

AB Objective: The primary objective of this phase I study was to define the safety profile of BAY 43-9006 administered in combination with doxorubicin. Patients and methods: Twenty-nine patients with advanced, refractory solid **tumors** were treated with doxorubicin (60mg/m2) every 3 wk for 6 consecutive cycles. BAY 43-9006 in combination with doxorubicin chemotherapy was administered at 3 dose levels. Results: Toxicity and response were evaluable in a total of 24 out of 29 enrolled patients. Dose-limiting toxicity was obsd. at various dose levels. Doxorubicin plasma Cmax/AUC values increased on escalating the dose of BAY 43-9006. Patients with liver **metastases** and elevated values of AST and conjugated bilirubin, compared to patients with normal hepatic function, showed a higher AUC for doxorubicin at all dose levels. Conclusions: Our data suggest a pharmacol. interaction of BAY 43-9006 at DL 400 mg bid with doxorubicin resulting in significantly increased AUC for doxorubicin.

ACCESSION NUMBER: 2004:12708 HCAPLUS

TITLE: A Phase I clinical and pharmacokinetic study of the Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with doxorubicin in patients with solid

tumors

AUTHOR(S): Richly, H.; Kupsch, P.; Passage, K.; Grubert, M.; Hilger, R. A.; Kredtke, S.; Voliotis, D.; Scheulen, M. E.; Seeber, S.; Strumberg, D.

CORPORATE SOURCE: West German Cancer Center, University of Essen, Essen, Germany

SOURCE: International Journal of Clinical Pharmacology and Therapeutics (2003), 41(12), 620-621
CODEN: ICTHEK; ISSN: 0946-1965

PUBLISHER: Dustri-Verlag Dr. Karl Feistle

DOCUMENT TYPE: Journal

LANGUAGE: English

TI . . . and pharmacokinetic study of the Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with doxorubicin in patients with solid **tumors**

AB . . . the safety profile of BAY 43-9006 administered in combination with doxorubicin. Patients and methods: Twenty-nine patients with advanced, refractory solid **tumors** were treated with doxorubicin (60mg/m2) every 3 wk for 6 consecutive cycles. BAY 43-9006 in combination with doxorubicin chemotherapy was. . . obsd. at various dose levels. Doxorubicin plasma Cmax/AUC values increased on escalating the dose of BAY 43-9006. Patients with liver **metastases** and elevated values of AST and conjugated bilirubin, compared to patients with normal hepatic function, showed a higher AUC for. . .

ST antitumor BAY439006 doxorubicin pharmacokinetic drug interaction solid **tumor**

IT Antitumor agents
Human
(clin. and pharmacokinetic study of Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with doxorubicin in patients with solid **tumors**)

IT Drug interactions
(pharmacokinetic; clin. and pharmacokinetic study of Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with doxorubicin in patients with solid **tumors**)

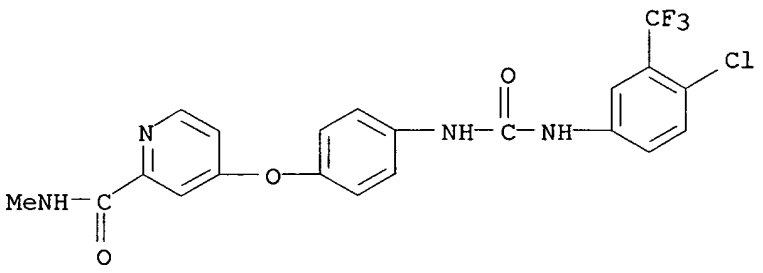
IT **Neoplasm**
(solid; clin. and pharmacokinetic study of Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with doxorubicin in patients with solid **tumors**)

IT 23214-92-8, Doxorubicin
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. and pharmacokinetic study of Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with doxorubicin in patients with solid **tumors**)

IT **284461-73-0**, BAY 43-9006
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. and pharmacokinetic study of Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with doxorubicin in patients with solid **tumors**)

IT 139691-76-2, Raf kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; clin. and pharmacokinetic study of Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with doxorubicin in patients with solid **tumors**)

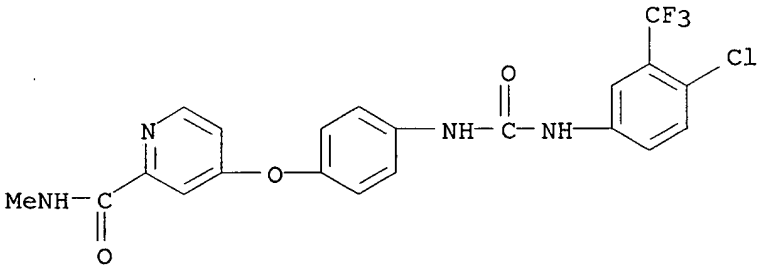
IT **284461-73-0,** BAY 43-9006
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. and pharmacokinetic study of Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with doxorubicin in patients with solid **tumors**)
RN 284461-73-0 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
AB Classical cytotoxic anticancer drugs generally have specific actions but also interfere with signalling pathways. A logical approach is therefore to combine the Raf kinase inhibitor (RKI) with classical cytotoxic agents since recent work has shown that the RKI BAY 43-9006 and CPT-11 have additive or synergistic actions. Objective: Because a pharmacol. drug-drug interaction cannot be ruled out, interaction studies were started using the RKI BAY 43-9006 in combination with the most important anticancer drugs, such as CPT-11. Patients and methods: The study protocol included three groups of 6 patients with solid **tumors** given different RKI doses and the same dosage of CPT-11. Blood samples for measurement of CPT-11 and SN-38 were obtained both during and in the absence of RKI treatment. Results: Ests. of toxicity, response and pharmacokinetics during the first RKI dose could be made in a total of 9/18 patients. All symptoms of toxicity were considered to be due to CPT-11 or RKI. The PK evaluation showed no significant differences for CPT-11 and SN-38, with or without RKI. Conclusions: The combination CPT-11 and SN-38 PK is not significantly influenced by the addn. of RKI. There is no indication that the PK of RKI are influenced significantly by CPT-11 and SN-38.

ACCESSION NUMBER:	2004:12707 HCAPLUS
TITLE:	Drug-drug interaction pharmacokinetic study with the Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with irinotecan (CPT-11) in patients with solid **tumors**
AUTHOR(S):	Mross, K.; Steinbild, S.; Baas, F.; Reil, M.; Buss, P.; Mersmann, S.; Voliotis, D.; Schwartz, B.; Brendel, E.
CORPORATE SOURCE:	Tumor Biology Center at the Albert-Ludwigs-University Freiburg, Leverkusen, Germany
SOURCE:	International Journal of Clinical Pharmacology and Therapeutics (2003), 41(12), 618-619 CODEN: ICTHEK; ISSN: 0946-1965
PUBLISHER:	Dustri-Verlag Dr. Karl Feistle

DOCUMENT TYPE: Journal
LANGUAGE: English
TI . . . pharmacokinetic study with the Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with irinotecan (CPT-11) in patients with solid **tumors**
AB . . . important anticancer drugs, such as CPT-11. Patients and methods: The study protocol included three groups of 6 patients with solid **tumors** given different RKI doses and the same dosage of CPT-11. Blood samples for measurement of CPT-11 and SN-38 were obtained. . .
ST antitumor BAY439006 irinotecan CPT11 pharmacokinetic drug interaction solid **tumor**
IT Human
(drug-drug interaction pharmacokinetic study with Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with irinotecan (CPT-11) in patients with solid **tumors**)
IT Drug interactions
(pharmacokinetic, none noted; drug-drug interaction pharmacokinetic study with Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with irinotecan (CPT-11) in patients with solid **tumors**)
IT **Neoplasm**
(solid; drug-drug interaction pharmacokinetic study with Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with irinotecan (CPT-11) in patients with solid **tumors**)
IT **284461-73-0**, BAY 43-9006
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug-drug interaction pharmacokinetic study with Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with irinotecan (CPT-11) in patients with solid **tumors**)
IT 86639-52-3, SN-38 100286-90-6, cpt-11
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug-drug interaction pharmacokinetic study with Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with irinotecan (CPT-11) in patients with solid **tumors**)
IT 139691-76-2, Raf kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; drug-drug interaction pharmacokinetic study with Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with irinotecan (CPT-11) in patients with solid **tumors**)
IT **284461-73-0**, BAY 43-9006
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug-drug interaction pharmacokinetic study with Raf kinase inhibitor (RKI) BAY 43-9006 administered in combination with irinotecan (CPT-11) in patients with solid **tumors**)
RN 284461-73-0 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

AB A review. BAY 43-9006 is the first orally active Raf kinase inhibitor to undergo clin. testing and has shown promise in the treatment of colorectal **cancer**. Treatment with BAY 43-9006 has resulted in stable disease in 37 % of patients across this phase I series, with 42 % of colorectal **cancer** patients achieving stable disease. Among patients achieving stable disease, 27 have been on therapy for over 6 mo without progression. Toxicity assocd. with this regimen is mild, with few grade 3/4 adverse events reported. Furthermore, fluorescence-activated cell sorter (FACS) anal. demonstrated that treatment with BAY 43-9006 could result in the inhibition of extracellular signal-regulated kinase (ERK) activation. Based on this phase I data, 2 phase II trials, including one in patients with colorectal **cancer**, have been initiated, and phase III trials are planned for 2003. At the 38th Annual Meeting of the American Society of Clin. Oncol., Vincent and colleagues reported on preclin. studies combining BAY 43-9006 with irinotecan, vinorelbine, or gemcitabine in human xenografts models. They demonstrated that BAY 43-9006 combined with cytotoxic or cytostatic agents is at least as efficacious as the individual agents administered alone. With this as rationale, multiple phase I/II studies are being designed to investigate the role of BAY 43-9006 in combination with std. chemotherapy.

ACCESSION NUMBER: 2003:476541 HCAPLUS
DOCUMENT NUMBER: 139:143192
TITLE: Activity of the Raf kinase inhibitor BAY 43-9006 in patients with advanced solid **tumors**
AUTHOR(S): DeGrendele, Heather
CORPORATE SOURCE: USA
SOURCE: Clinical Colorectal Cancer (2003), 3(1), 16-18
CODEN: CCCLCF; ISSN: 1533-0028
PUBLISHER: Cancer Information Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

TI Activity of the Raf kinase inhibitor BAY 43-9006 in patients with advanced solid **tumors**

AB . . . the first orally active Raf kinase inhibitor to undergo clin. testing and has shown promise in the treatment of colorectal **cancer**. Treatment with BAY 43-9006 has resulted in stable disease in 37 % of patients across this phase I series, with 42 % of colorectal **cancer** patients achieving stable disease. Among patients achieving stable disease, 27 have been on therapy for over 6 mo without progression.. . . signal-regulated kinase (ERK) activation. Based on this phase I data, 2 phase II trials, including one in patients with colorectal **cancer**, have been initiated, and phase III trials are planned for 2003. At the 38th Annual Meeting of the American Society. . .

ST review Raf kinase inhibitor BAY439006 antitumor colorectal **tumor** ; BAY439006 pharmacokinetics antitumor solid **tumor** review

IT Antitumor agents
Human
(activity of Raf kinase inhibitor BAY 43-9006 in patients with advanced solid **tumors**)

IT Intestine, **neoplasm**
(colorectal; activity of Raf kinase inhibitor BAY 43-9006 in patients with advanced solid **tumors**)

IT **Neoplasm**
(solid; activity of Raf kinase inhibitor BAY 43-9006 in patients with advanced solid **tumors**)

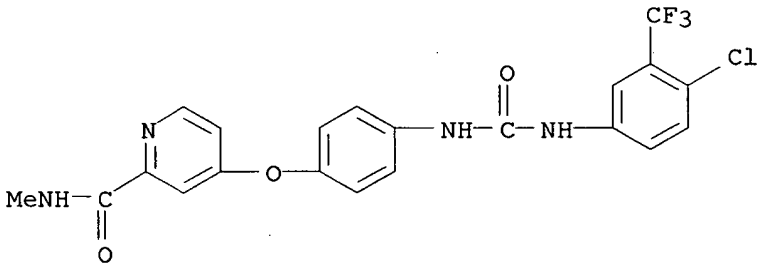
IT **284461-73-0**, BAY 43-9006
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activity of Raf kinase inhibitor BAY 43-9006 in patients with advanced solid **tumors**)

IT 139691-76-2, Raf kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; activity of Raf kinase inhibitor BAY 43-9006 in patients with advanced solid **tumors**)

IT **284461-73-0**, BAY 43-9006
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activity of Raf kinase inhibitor BAY 43-9006 in patients with advanced solid **tumors**)

RN 284461-73-0 HCAPLUS

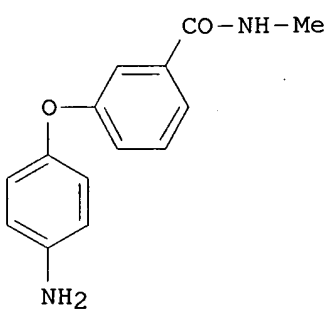
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



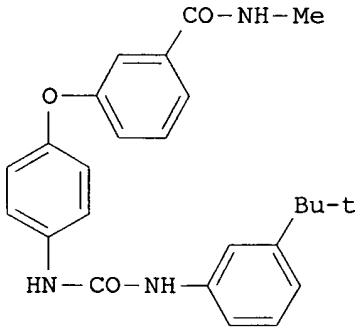
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4

GI



II



III

AB Title compds. B-NHCONH-L-(M-L1)q (I) [B = (un)substituted pyridyl, quinolinyl, isoquinolinyl; L = 5 or 6 membered cyclic structure; L1 = substituted cyclic moiety having at least 5 members; M = bridging group having at least one atom; q = 1-3; with proviso that L and L1 contain 0-4 hetero atoms, e.g., N, O and S] and their pharmaceutically acceptable salts were prepd. For example, coupling of aniline II, e.g., prepd. from Et 3-hydroxybenzoate in 4-steps, with bis(trichloromethyl)carbonate followed by 3-tert-butylaniline afforded urea III. In in vitro raf kinase assays, 112-specific examples of compds. I inhibited kinase activity with IC50 values ranging from 10 nM-10 .mu.M. Compds. I are useful for the treatment of **cancerous** cell growth mediated by raf kinase.

ACCESSION NUMBER: 2002:850357 HCAPLUS
DOCUMENT NUMBER: 137:352907
TITLE: Preparation of quinolyl, isoquinolyl or pyridyl-ureas as inhibitors of raf kinase for the treatment of **tumors** and/or **cancerous** cell growth
INVENTOR(S): Dumas, Jacques; Riedl, Bernd; Khire, Uday; Wood, Jill E.; Robert, Sibley N.; Monahan, Mary-Katherine; Renick, Joel; Gunn, David E.; Lowinger, Timothy B.; Scott, William J.; Smith, Roger A.
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 63 pp., Cont.-in-part of U.S. Ser. No. 758,548.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002165394	A1	20021107	US 2001-777920	20010207
US 2002137774	A1	20020926	US 2001-907970	20010719
WO 2002062763	A2	20020815	WO 2002-US3361	20020207
WO 2002062763	A3	20021010		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003139605 A1 20030724 US 2002-71248 20020211

PRIORITY APPLN. INFO.: US 1999-115877P P 19990113
US 1999-257266 B2 19990225
US 1999-425228 B2 19991022
US 2001-758548 A2 20010112
US 1999-115878P P 19990113
US 2001-777920 A 20010207
US 2001-948915 A1 20010910

OTHER SOURCE(S): MARPAT 137:352907

TI Preparation of quinolyl, isoquinolyl or pyridyl-ureas as inhibitors of raf kinase for the treatment of **tumors** and/or **cancerous** cell growth

AB . . . I inhibited kinase activity with IC50 values ranging from 10 nM-10 .mu.M. Compds. I are useful for the treatment of **cancerous** cell growth mediated by raf kinase.

IT Antitumor agents
Combinatorial chemistry
Human
Neoplasm
Solid phase synthesis
(prepn. of quinolyl, isoquinolyl or pyridyl-ureas as inhibitors of raf kinase)

IT 228418-48-2P 284461-33-2P 284461-34-3P 284461-35-4P 284461-36-5P
284461-37-6P 284461-38-7P 284461-39-8P 284461-40-1P 284461-41-2P
284461-42-3P 284461-43-4P 284461-44-5P 284461-45-6P 284461-46-7P
284461-47-8P 284461-48-9P 284461-49-0P 284461-50-3P 284461-51-4P
284461-52-5P 284461-53-6P 284461-54-7P 284461-55-8P 284461-56-9P
284461-57-0P 284461-58-1P 284461-59-2P 284461-60-5P 284461-61-6P
284461-62-7P 284461-63-8P 284461-64-9P 284461-65-0P 284461-66-1P
284461-67-2P 284461-68-3P 284461-69-4P 284461-70-7P 284461-71-8P
284461-72-9P **284461-73-0P** 284461-74-1P 284461-75-2P
284461-76-3P 284461-77-4P **284461-78-5P** 284461-79-6P
284461-80-9P 284461-81-0P 284461-82-1P 284461-84-3P
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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of quinolyl, isoquinolyl or pyridyl-ureas as inhibitors of raf kinase)

IT **284461-73-0P 284461-78-5P 284461-80-9P**
284462-28-8P 284462-29-9P 284462-30-2P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of quinolyl, isoquinolyl or pyridyl-ureas as inhibitors of raf kinase)

RN 284461-73-0 HCAPLUS
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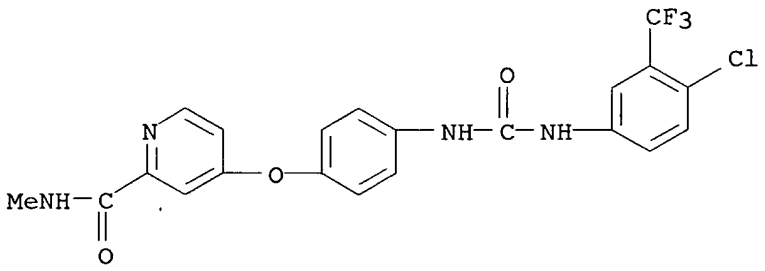

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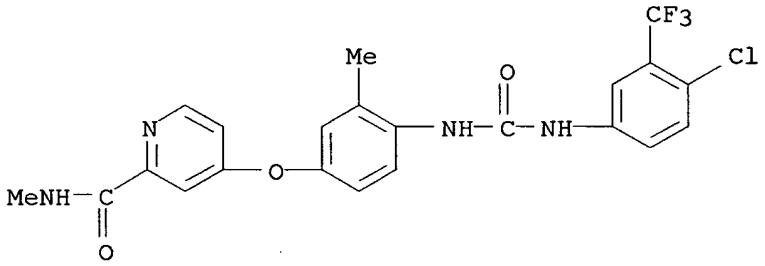

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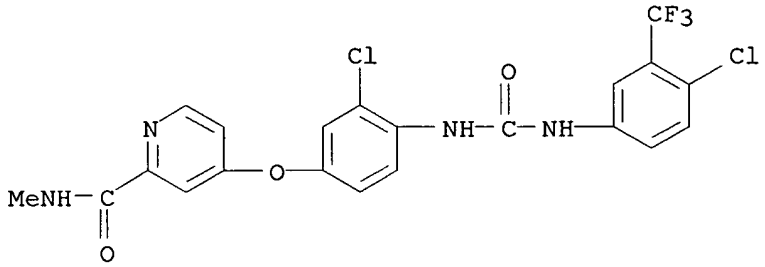

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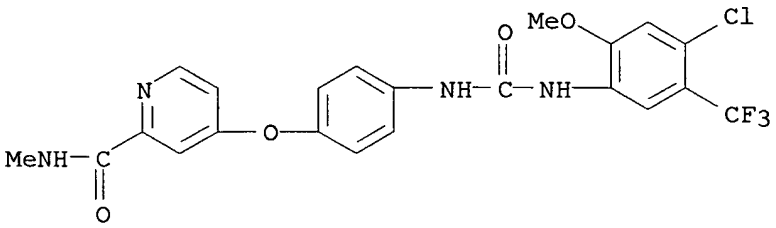
INDEX NAME)



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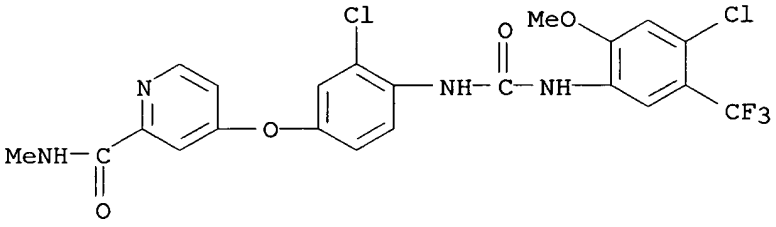

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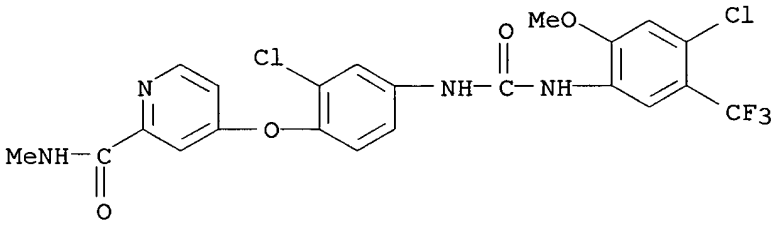

L9 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
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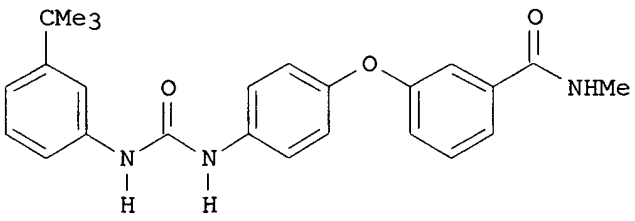

II

AB Title compds., e.g., RNHCONHZOR1 [I; R = C6H4(CMe3)-3, 2-methoxy-5-trifluoromethylphenyl, 4-chloro-3-trifluoromethylphenyl, 2-methoxy-3-quinolyl, etc.; R1 = (un)substituted acylphenyl, -acylpyridinyl, etc.; Z = (un)substituted 1,3- or -1,4-phenylene] were prepd. Thus, 4-(H2N)C6H4OC6H4(CONHMe)-4 (prepn. given) was condensed with 3-(Me3C)C6H4NH2 and CO(OCCl3)2 to give title compd. II. Data for biol. activity of title compds. were given.

ACCESSION NUMBER: 2002:615574 HCAPLUS
DOCUMENT NUMBER: 137:169425
TITLE: Preparation of N-aryl-N'-[(acylphenoxy)phenyl]ureas as raf kinase inhibitors
INVENTOR(S): Dumas, Jacques; Riedl, Bernd; Khire, Uday; Wood, Jill E.; Sibley, Robert N.; Monahan, Mary-Katherine; Renick, Joel; Gunn, David E.; Lowinger, Timothy B.; Scott, William J.; Smith, Roger A.
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002062763	A2	20020815	WO 2002-US3361	20020207
WO 2002062763	A3	20021010		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002165394	A1	20021107	US 2001-777920	20010207

PRIORITY APPLN. INFO.:

US 2001-777920	A	20010207
US 1999-115877P	P	19990113
US 1999-257266	B2	19990225
US 1999-425228	B2	19991022
US 2001-758548	A2	20010112

OTHER SOURCE(S): MARPAT 137:169425

IT **Neoplasm**
(treatment; prepn. of N-aryl-N'-[(acylphenoxy)phenyl]ureas as raf kinase inhibitors)

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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-aryl-N'-[(acylphenoxy)phenyl]ureas as raf kinase inhibitors)

IT **284461-73-0P 284461-78-5P 284461-80-9P**
284461-83-2P 284462-28-8P 284462-29-9P
284462-30-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-aryl-N'-[(acylphenoxy)phenyl]ureas as raf kinase inhibitors)

RN 284461-73-0 HCAPLUS
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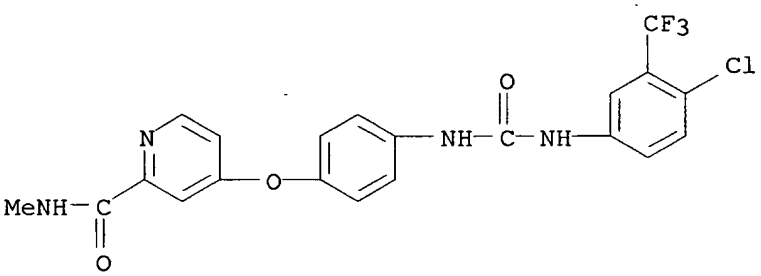

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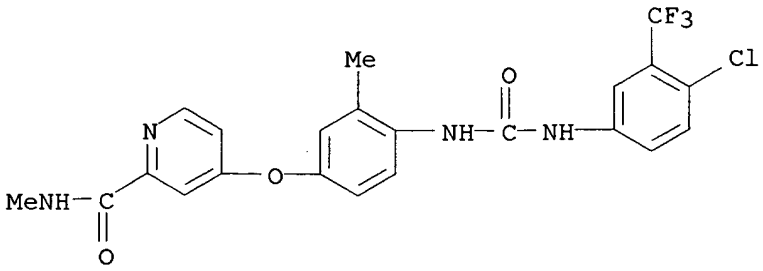

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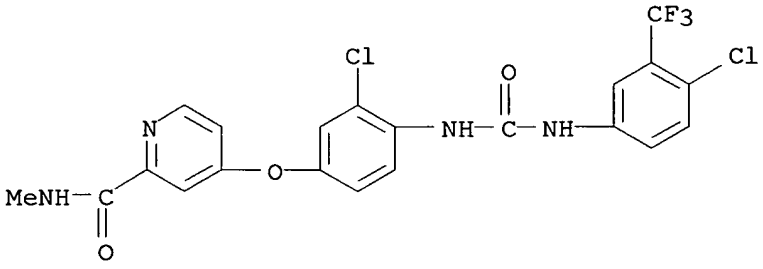

RN 284461-83-2 HCAPLUS
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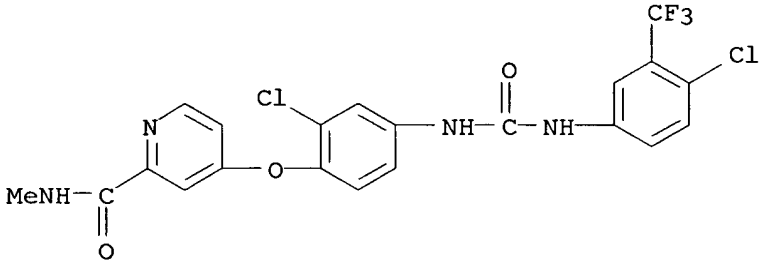

RN 284462-28-8 HCAPLUS
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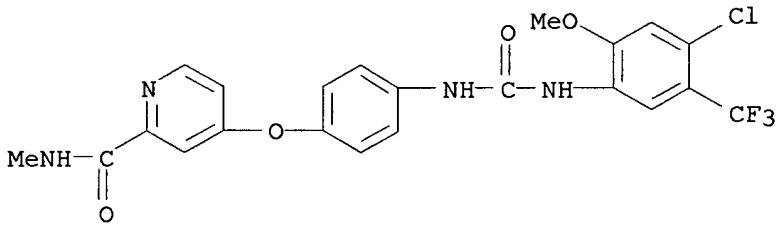

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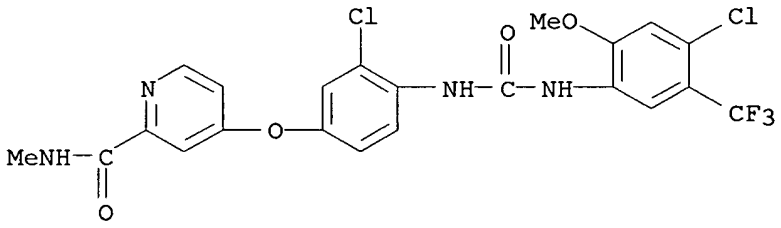

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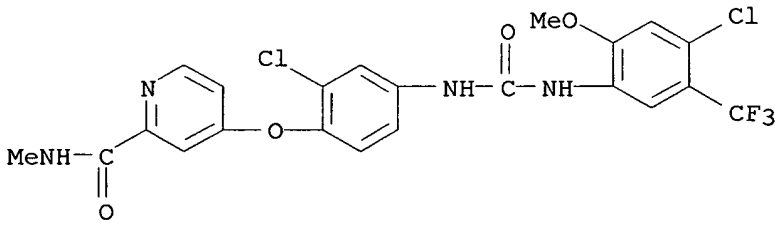

L9 ANSWER 18 OF 29 USPATFULL on STN
AB This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:251820 USPATFULL
TITLE: Carboxyaryl substituted diphenyl ureas as raf kinase inhibitors
INVENTOR(S): Riedl, Bernd, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Dumas, Jacques, Orange, CT, UNITED STATES
Khire, Uday, Hamden, CT, UNITED STATES
Lowinger, Timothy B., Nishinomiya City, CANADA
Scott, William J., Guilford, CT, UNITED STATES

Smith, Roger A., Madison, CT, UNITED STATES
Wood, Jill E., Hamden, CT, UNITED STATES
Monahan, Mary-Katherine, Hamden, CT, UNITED STATES
Natero, Reina, Hamden, CT, UNITED STATES
Renick, Joel, San Diego, CA, UNITED STATES
Sibley, Robert N., North Haven, CT, UNITED STATES
PATENT ASSIGNEE(S): BAYER CORPORATION, Pittsburgh, PA (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002137774	A1	20020926	
APPLICATION INFO.:	US 2001-907970	A1	20010719	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115877P	19990113 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS: 67
EXEMPLARY CLAIM: 1
LINE COUNT: 3732
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0002] The p21.sup.ras oncogene is a major contributor to the development and progression of human solid **cancers** and is mutated in 30% of all human **cancers** (Bolton et al. Ann. Rep. Med. Chem. 1994, 29, 165-74;Bos. **Cancer** Res. 1989, 49, 4682-9). In its normal, unmutated form, the ras protein is a key element of the signal transduction. . . . GDP-bound resting form is strictly controlled by ras' endogenous GTPase activity and other regulatory proteins. In the ras mutants in **cancer** cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the **cancerous** growth of the cells which carry these mutants (Magnuson et al. Semin. **Cancer** Biol. 1994, 5, 247-53). It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase. . . . antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human **tumor** types (Monia et al., Nat. Med. 1996, 2, 668-75).

SUMM . . . compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of **tumors** and/or **cancerous** cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal solid **cancers**, e.g., murine **cancer**, since the progression of these **cancers** is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compounds of the invention are useful in treating **cancers**, including solid **cancers**, such as, for example, **carcinomas** (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).

SUMM . . . is directed to compounds which inhibit the enzyme raf kinase and also compounds, compositions and methods for the treatment of

cancerous cell growth mediated by raf kinase wherein a compound of Formula I is administered or pharmaceutically acceptable salt thereof.

DETD [0341] For in vitro growth assay, human **tumor** cell lines, including but not limited to HCT116 and DLD-1, containing mutated K-ras genes were used in standard proliferation assays for anchorage dependent growth on plastic or anchorage independent growth in soft agar. Human **tumor** cell lines were obtained from ATCC (Rockville Md.) and maintained in RPMI with 10% heat inactivated fetal bovine serum and. . .

DETD [0344] An in vivo assay of the inhibitory effect of the compounds on **tumors** (e.g., solid **cancers**) mediated by raf kinase can be performed as follows:

DETD . . . mice are dosed i.p., i.v. or p.o. at 10, 30, 100, or 300 mg/Kg beginning on approximately day 10, when **tumor** size is between 50-100 mg. Animals are dosed for 14 consecutive days once a day; **tumor** size was monitored with calipers twice a week.

DETD [0346] The inhibitory effect of the compounds on raf kinase and therefore on **tumors** (e.g., solid **cancers**) mediated by raf kinase can further be demonstrated in vivo according to the technique of Monia et al. (Nat. Med.. . .

CLM What is claimed is:

62. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 1.

63. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 33.

64. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 38.

65. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 39.

66. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of 3-tert butyl phenyl ureas. . .

67. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of the 3-tert butyl phenyl. . .

IT 228418-48-2P 284461-33-2P 284461-34-3P 284461-35-4P 284461-36-5P
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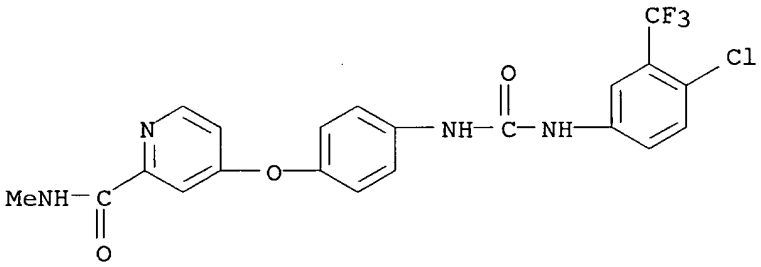
284462-36-8P 284462-70-0P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

IT **284461-73-0P 284461-78-5P 284461-80-9P**
284461-83-2P 284462-28-8P 284462-29-9P
284462-30-2P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

RN 284461-73-0 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-78-5 USPATFULL
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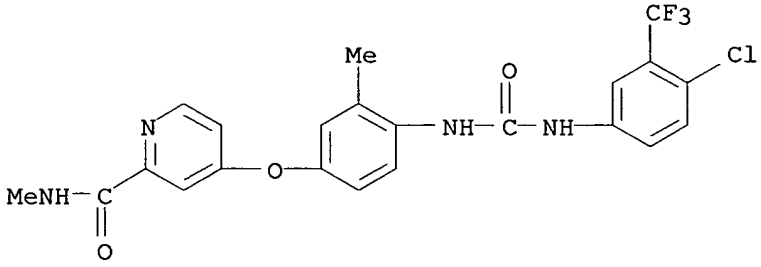

RN 284461-80-9 USPATFULL
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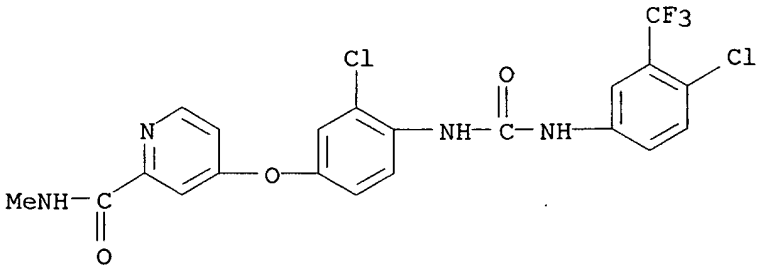

RN 284461-83-2 USPATFULL
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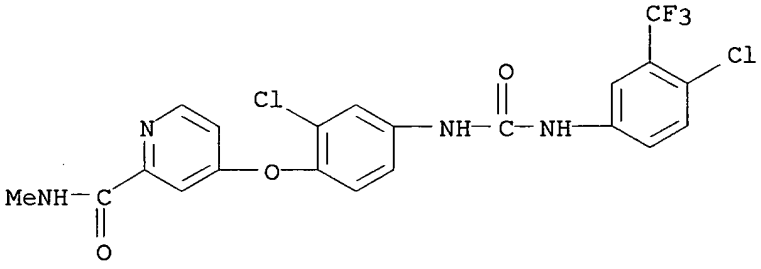

RN 284462-28-8 USPATFULL
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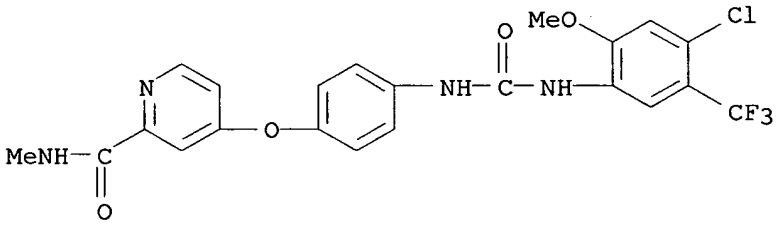
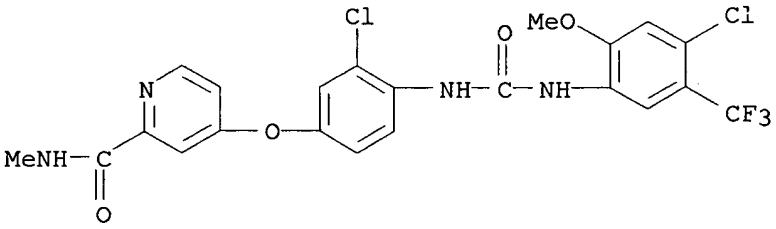
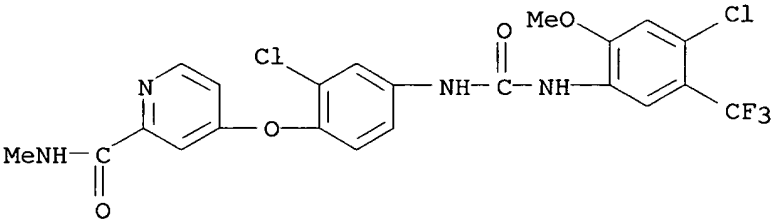


RN 284462-29-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 19 OF 29 USPATFULL on STN
AB This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:78859 USPATFULL
TITLE:	Omega-carboxyaryl substituted diphenyl ureas as raf kinase inhibitors
INVENTOR(S):	Uday, Khire, Hamden, CT, UNITED STATES Dumas, Jacques, Orange, CT, UNITED STATES Riedl, Bernd, Wuppertal, GERMANY, FEDERAL REPUBLIC OF Lowinger, Timothy B., Nishinomiya City, JAPAN Scott, William J., Guilford, CT, UNITED STATES Smith, Roger A., Madison, CT, UNITED STATES Wood, Jill E., Hamden, CT, UNITED STATES Monahan, Mary-Katherine, Hamden, CT, UNITED STATES Natero, Reina, Hamden, CT, UNITED STATES Joel, Renick, Milford, CT, UNITED STATES Sibley, Robert N., North Haven, CT, UNITED STATES
PATENT ASSIGNEE(S):	BAYER CORPORATION, Pittsburgh, PA, 15205 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042517	A1	20020411
APPLICATION INFO.:	US 2001-948915	A1	20010910 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-425228, filed on 22 Oct 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-257266, filed on 25 Feb 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115877P	19990113 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201	
NUMBER OF CLAIMS:	67	
EXEMPLARY CLAIM:	1	
LINE COUNT:	3675	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0003] The p21.sup.ras oncogene is a major contributor to the development and progression of human solid **cancers** and is mutated in 30% of all human **cancers** (Bolton et al. Ann. Rep. Med. Chem. 1994, 29, 165-74; Bos. **Cancer** Res. 1989, 49, 4682-9). In its normal, unmutated form, the ras protein is a key element of the signal transduction. . . . GDP-bound resting form is strictly controlled by ras' endogenous GTPase activity and other regulatory proteins. In the ras mutants in **cancer** cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the **cancerous** growth of the cells which carry these mutants (Magnuson et al. Semin. **Cancer** Biol. 1994, 5, 247-53). It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase. . . . antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human **tumor** types (Monia et al., Nat. Med. 1996, 2, 668-75).

SUMM . . . compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of **tumors** and/or **cancerous** cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal solid **cancers**, e.g., murine **cancer**, since the progression of these **cancers** is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compounds of the invention are useful in treating **cancers**, including solid **cancers**, such as, for example, **carcinomas** (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).

SUMM . . . is directed to compounds which inhibit the enzyme raf kinase and also compounds, compositions and methods for the treatment of **cancerous** cell growth mediated by raf kinase wherein a compound of Formula I is administered or pharmaceutically acceptable salt thereof.

CLM What is claimed is:

62. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 1.

63. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 33.

64. A method for the treatment of a **cancerous** cell growth

mediated by raf kinase, comprising administering a compound of Formula I of claim 38.

65. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 39.

66. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of 3-tert butyl phenyl ureas. . .

67. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of the 3-tert butyl phenyl. . .

IT 228418-48-2P 284461-33-2P 284461-34-3P 284461-35-4P 284461-36-5P
284461-37-6P 284461-38-7P 284461-39-8P 284461-40-1P 284461-41-2P
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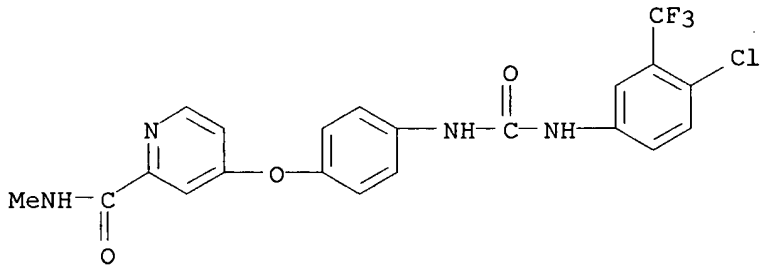
284462-31-3P 284462-32-4P 284462-33-5P 284462-34-6P 284462-35-7P
284462-36-8P 284462-70-0P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

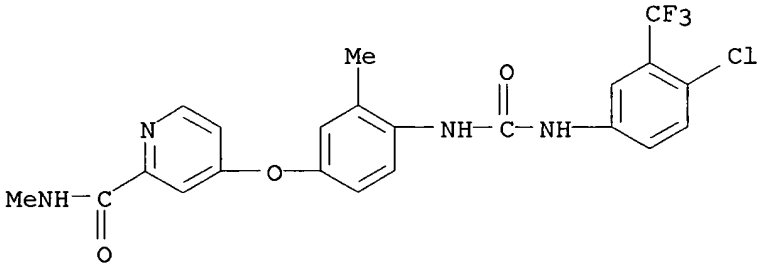
IT **284461-73-0P 284461-78-5P 284461-80-9P**
284461-83-2P 284462-28-8P 284462-29-9P
284462-30-2P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

RN 284461-73-0 USPATFULL

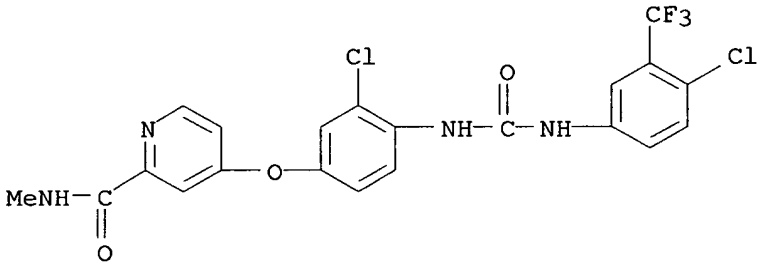
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



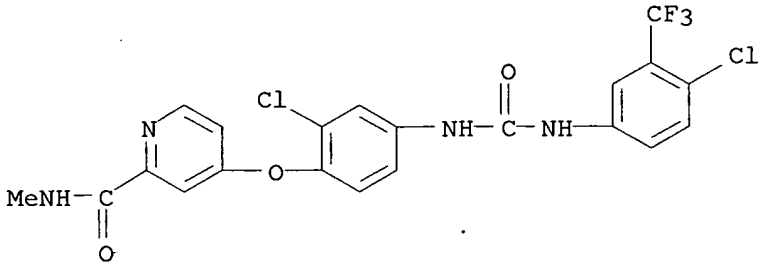
RN 284461-78-5 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-methylphenoxy]-N-methyl- (9CI) (CA INDEX NAME)



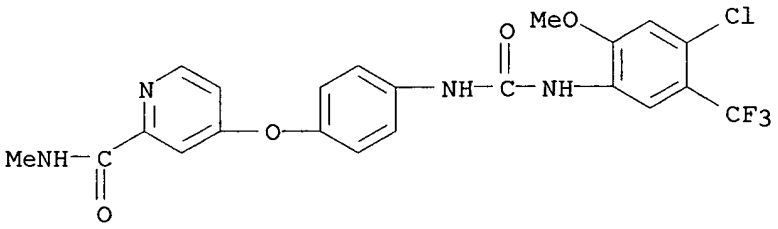
RN 284461-80-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



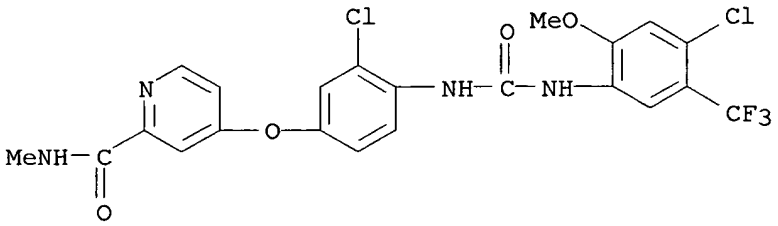
RN 284461-83-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



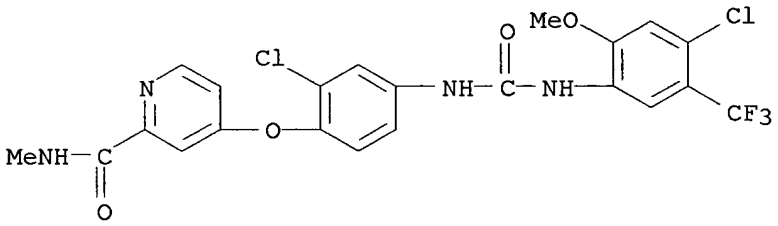
RN 284462-28-8 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-29-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)

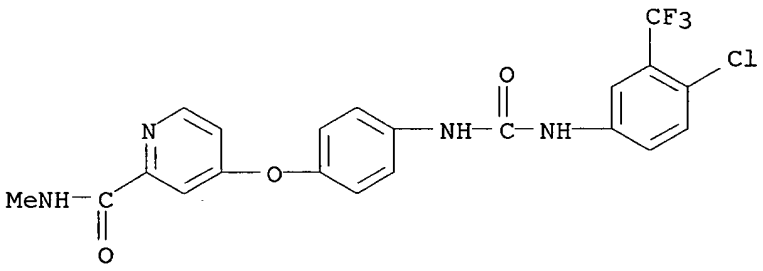


RN 284462-30-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
AB A review. The drug design and discovery efforts described in the previous section led to the development of a novel, small mol. Raf-1 kinase inhibitor, BAY 43-9006, which belongs to a class that can be broadly described as bis-aryl ureas. BAY 43-9006 was identified during a large medicinal chem. optimization program, and this compd. was selected for further pharmacol. characterization based on its potent inhibition of Raf-1 (IC50 12 nM) and its favorable kinase selectivity profile [2, 3]. In vitro and in vivo expts. were designed to demonstrate effective blockade of the Raf/MEK/ERK signaling pathway in **tumor** cells and for antitumor efficacy in human xenograft models.
ACCESSION NUMBER: 2002:785445 HCAPLUS
DOCUMENT NUMBER: 138:296904
TITLE: BAY 43-9006: Preclinical data

AUTHOR(S): Wilhelm, Scott; Chien, Du-Shieng
CORPORATE SOURCE: Bayer Research Center, Institute for Preclinical Drug Development, Pharmaceutical Division, Bayer Corporation, West Haven, CT, 06516, USA
SOURCE: Current Pharmaceutical Design (2002), 8(25), 2255-2257
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB . . . [2, 3]. In vitro and in vivo expts. were designed to demonstrate effective blockade of the Raf/MEK/ERK signaling pathway in **tumor** cells and for antitumor efficacy in human xenograft models.
IT Antitumor agents
Human
Neoplasm
(antitumor BAY 43-9006)
IT **284461-73-0**, BAY 43-9006
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor BAY 43-9006)
IT **284461-73-0**, BAY 43-9006
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor BAY 43-9006)
RN 284461-73-0 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
AB A review. Various signaling pathways can confer the malignant phenotype to a cell. Ras signaling proteins have been found to play an important role in controlling cellular growth. Raf-1 is a protein kinase that exerts its effects downstream of Ras in the mitogen-activated protein kinase pathway and is thus likely to be crucial in the development of the malignant phenotype. BAY 43-9006 is an orally administered selective inhibitor of Raf-1 and the first compd. of its class to enter clin. trials. This article describes the early clin. data of BAY 43-9006 in patients with advanced, refractory solid **tumors**. To date, over 60 patients have been treated as part of four Phase I clin. trials. Dose levels have ranged from 50mg once weekly to 200mg twice-daily in continuous administration. The drug has been generally well tolerated with no dose limiting toxicity yet encountered. The more common

toxicities have involved the gastrointestinal tract (diarrhea, nausea, abdominal cramping) and the skin (pruritus, rash, cheilitis). Pharmacokinetic evaluations have found BAY 43-9006 to have considerable interpatient variability. However, there seems to be an increase in Cmax and AUC values with increasing dose. There is no clear effect of food on bioavailability. Splitting the dose to twice-daily administration has shown increases in Cmax and AUC values but is also accompanied by considerable interpatient variability.

ACCESSION NUMBER: 2002:785444 HCAPLUS
DOCUMENT NUMBER: 137:362317
TITLE: BAY 43-9006: Early clinical data in patients with advanced solid malignancies
AUTHOR(S): Hotte, Sebastien J.; Hirte, Hal W.
CORPORATE SOURCE: Department of Medicine, Hamilton Regional Cancer Centre, McMaster University and Division of Medical Oncology, Hamilton, ON, Can.
SOURCE: Current Pharmaceutical Design (2002), 8(25), 2249-2253
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB . . . to enter clin. trials. This article describes the early clin. data of BAY 43-9006 in patients with advanced, refractory solid **tumors**. To date, over 60 patients have been treated as part of four Phase I clin. trials. Dose levels have ranged. . .

ST review antitumor BAY439006 drug bioavailability solid **neoplasm**

IT Drug bioavailability
Human
(BAY 43-9006 for patients with advanced solid **neoplasm**)

IT Antitumor agents
(solid **neoplasm**; BAY 43-9006 for patients with advanced solid **neoplasm**)

IT **Neoplasm**
(solid; BAY 43-9006 for patients with advanced solid **neoplasm**)

IT **475207-59-1**, BAY 43-9006 mono-p-tosylate
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BAY 43-9006 for patients with advanced solid **neoplasm**)

IT 139691-76-2, Raf-1 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; BAY 43-9006 for patients with advanced solid **neoplasm**)

IT **475207-59-1**, BAY 43-9006 mono-p-tosylate
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BAY 43-9006 for patients with advanced solid **neoplasm**)

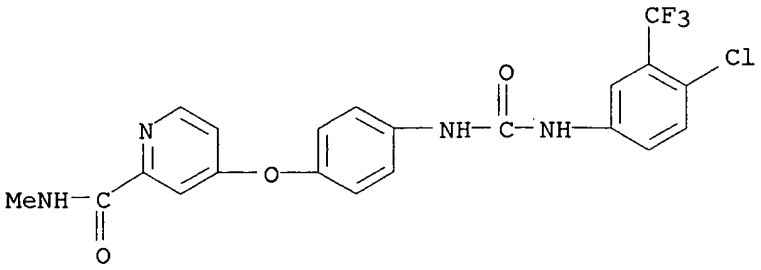
RN 475207-59-1 HCAPLUS

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-, mono(4-methylbenzenesulfonate) (9CI) (CA INDEX NAME)

CM 1

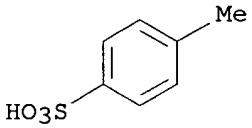
CRN 284461-73-0

CMF C21 H16 Cl F3 N4 O3



CM 2

CRN 104-15-4
CMF C7 H8 O3 S



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

AB A review with refs. The Ras/Raf/MEK pathway is a signaling module that controls cell growth and survival. Activation of this pathway results in a cascade of events from the cell surface to the nucleus ultimately affecting cellular proliferation, apoptosis, differentiation and transformation. Raf is a serine/threonine kinase that is a downstream effector enzyme of Ras. When activated, Raf goes on to activate MEK1 and MEK2 kinases which in turn phosphorylate and activate ERK1 and ERK2 which translocate to the nucleus where they stimulate pathways required for translation initiation and transcription activation leading to proliferation. Raf kinase has been validated as a potential and attractive target for hyperproliferative disorders such as **cancer**. Research has recently focused on efforts to discover potent Raf kinase inhibitors and several low-mol.-wt. Raf kinase inhibitors have been described. Bis-aryl ureas were identified within this program using medicinal chem.-directed syntheses or combinatorial libraries. After high-throughput screening of more than 200,000 compds. against recombinant Raf-1 kinase, the orally active Bay-43-9006 was identified as having potent inhibitory activity and was chosen for further development as a treatment for **cancer**. Bay-43-9006 has exhibited potent in vitro activity against several **tumor** cell lines and has displayed efficacy in human **tumor** xenograft models. Moreover, results from phase I development in patients with a variety of **cancer** types indicates promising clin. efficacy for the compd.

ACCESSION NUMBER: 2003:208292 HCAPLUS
DOCUMENT NUMBER: 139:269975

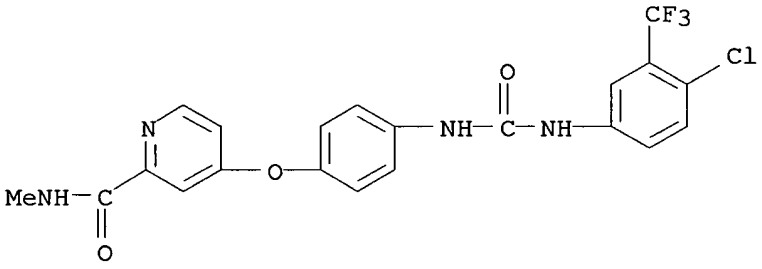
TITLE: Oncolytic Raf kinase inhibitor
AUTHOR(S): Sorbera, L. A.; Castaner, J.; Bozzo, J.; Leeson, P. A.
CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (2002), 27(12), 1141-1147
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB . . . activation leading to proliferation. Raf kinase has been validated as a potential and attractive target for hyperproliferative disorders such as **cancer**. Research has recently focused on efforts to discover potent Raf kinase inhibitors and several low-mol.-wt. Raf kinase inhibitors have been. . . orally active Bay-43-9006 was identified as having potent inhibitory activity and was chosen for further development as a treatment for **cancer**. Bay-43-9006 has exhibited potent in vitro activity against several **tumor** cell lines and has displayed efficacy in human **tumor** xenograft models. Moreover, results from phase I development in patients with a variety of **cancer** types indicates promising clin. efficacy for the compd.

IT 139691-76-2, Raf kinase **284461-73-0**, Bay-43-9006
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oncolytic Raf kinase inhibitor)

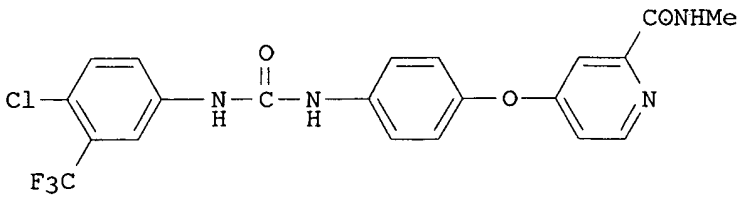
IT **284461-73-0**, Bay-43-9006
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oncolytic Raf kinase inhibitor)

RN 284461-73-0 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
GI



I

AB Urea I (BAY 43-9006), a potent Raf kinase inhibitor, was prepd. in four steps from picolinic acid with an overall yield of 63%. Significant process research enabled isolation of each intermediate and target without chromatog. purifn., and overall yield increases >50% were obsd. compared to those from previous methods. This report focuses on improved synthetic strategies for prodn. of scaled quantities of I for preclin., toxicol. studies. These improvements may be useful to assemble other urea targets as potential therapeutic agents to combat **cancer**.

ACCESSION NUMBER: 2002:713341 HCAPLUS
DOCUMENT NUMBER: 137:384728
TITLE: A Scaleable Synthesis of BAY 43-9006: A Potent Raf Kinase Inhibitor for the Treatment of **Cancer**
AUTHOR(S): Bankston, Donald; Dumas, Jacques; Natero, Reina; Riedl, Bernd; Monahan, Mary-Katherine; Sibley, Robert
CORPORATE SOURCE: Pharmaceutical Division, Bayer Research Center, West Haven, CT, 06516, USA
SOURCE: Organic Process Research & Development (2002), 6(6), 777-781
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

TI A Scaleable Synthesis of BAY 43-9006: A Potent Raf Kinase Inhibitor for the Treatment of **Cancer**

AB . . . for preclin., toxicol. studies. These improvements may be useful to assemble other urea targets as potential therapeutic agents to combat **cancer**.

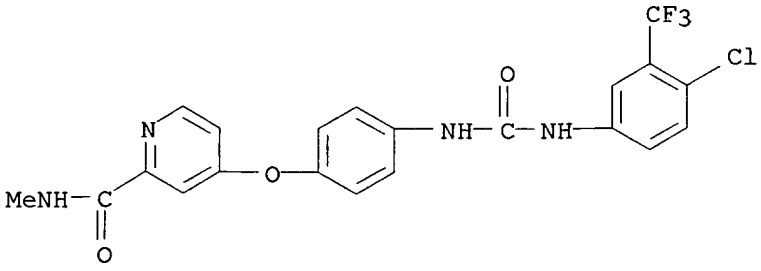
ST Raf kinase inhibitor treatment **cancer** scaleable synthesis; manuf BAY 439006; pyridinyloxyphenylurea manuf

IT **284461-73-0P**, BAY 43-9006
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(scalable four-step synthesis of a Raf kinase inhibitor urea BAY 43-9006 from picolinic acid)

IT **284461-73-0P**, BAY 43-9006
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(scalable four-step synthesis of a Raf kinase inhibitor urea BAY 43-9006 from picolinic acid)

RN 284461-73-0 HCAPLUS

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 24 OF 29 USPATFULL on STN

AB This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2001:188813 USPATFULL

TITLE: Omega-carboxyaryl substituted diphenyl ureas as raf kinase inhibitors

INVENTOR(S): Riedl, Bernd, Wupperal, Germany, Federal Republic of
Dumas, Jacques, Orange, CT, United States
Khire, Uday, Hamden, CT, United States
Lowinger, Timothy P., Nashnomya City, Japan
Scott, William J., Gulford, CT, United States
Smith, Roger A., Madison, CT, United States
Wood, Jill E., Hamden, CT, United States
Monahan, Mary-Katherine, Hamden, CT, United States
Natero, Rena, Handen, CT, United States
Renick, Joel, Milford, CT, United States
Sibley, Robert N., North Haven, CT, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001034447	A1	20011025
APPLICATION INFO.:	US 2001-773604	A1	20010202 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-425228, filed on 22 Oct 1999, PENDING Continuation-in-part of Ser. No. US 1999-257266, filed on 25 Feb 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115877P	19990113 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201

NUMBER OF CLAIMS: 67

EXEMPLARY CLAIM: 1

LINE COUNT: 3666

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0002] The p21.sup.ras oncogene is a major contributor to the development and progression of human solid **cancers** and is mutated in 30% of all human **cancers** (Bolton et al. Ann. Rep.

Med. Chem. 1994, 29, 165-74; Bos. **Cancer** Res. 1989, 49, 4682-9). In its normal, umnutated form, the ras protein is a key element of the signal transduction. . . GDP-bound resting form is strictly controlled by ras' endogenous GTPase activity and other regulatory proteins. In the ras mutants in **cancer** cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the **cancerous** growth of the cells which carry these mutants (Magnuson et al. Semin. **Cancer** Biol. 1994, 5, 247-53). It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase. . . antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human **tumor** types (Monia et al., Nat. Med. 1996, 2, 668-75).

SUMM . . . compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of **tumors** and/or **cancerous** cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal solid **cancers**, e.g., murine **cancer**, since the progression of these **cancers** is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compounds of the invention are useful in treating **cancers**, including solid **cancers**, such as, for example, **carcinomas** (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).

SUMM . . . is directed to compounds which inhibit the enzyme raf kinase and also compounds, compositions and methods for the treatment of **cancerous** cell growth mediated by raf kinase wherein a compound of Formula I is administered or pharmaceutically acceptable salt thereof.

CLM What is claimed is:

62. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 1.

63. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 33.

64. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 38.

65. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 39.

66. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of 3-tert butyl phenyl ureas. . .

67. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of the 3-tert butyl phenyl. . .

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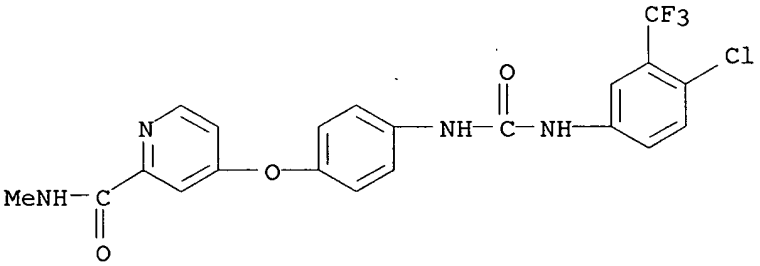
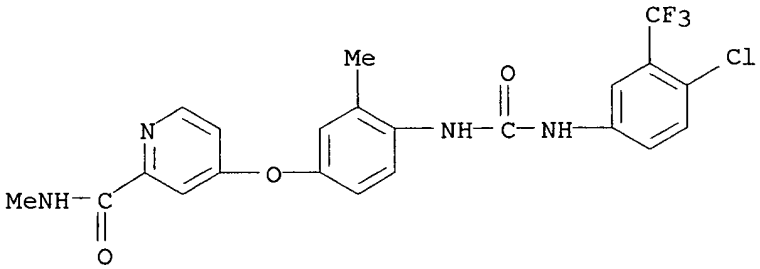
284462-31-3P 284462-32-4P 284462-33-5P 284462-34-6P 284462-35-7P
284462-36-8P 284462-70-0P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

IT **284461-73-0P 284461-78-5P 284461-80-9P**
284461-83-2P 284462-28-8P 284462-29-9P
284462-30-2P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

RN 284461-73-0 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-78-5 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-methylphenoxy]-N-methyl- (9CI) (CA INDEX NAME)



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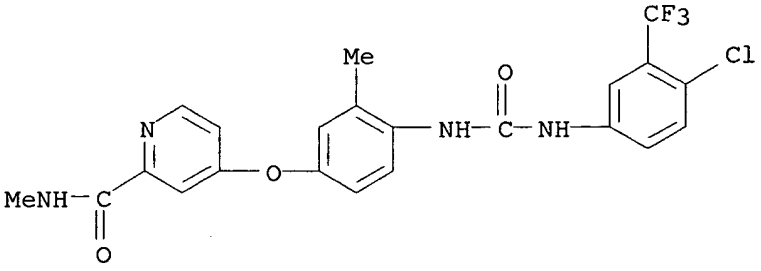
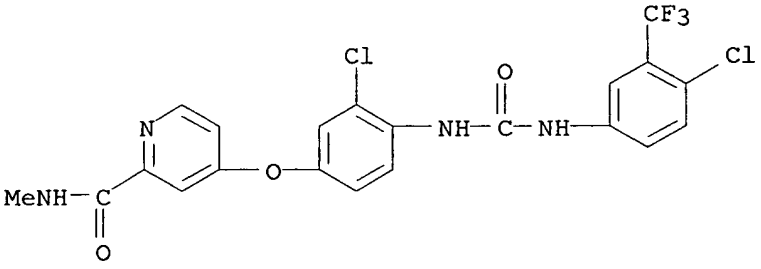


RN 284461-80-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-83-2 USPATFULL
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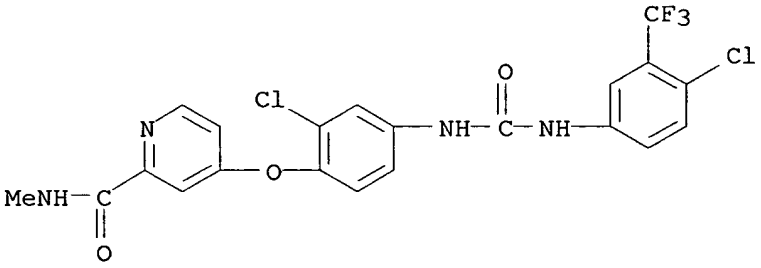
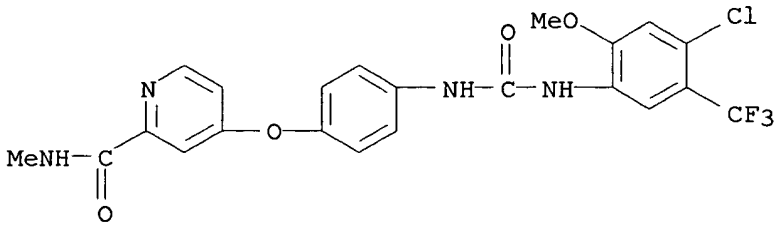
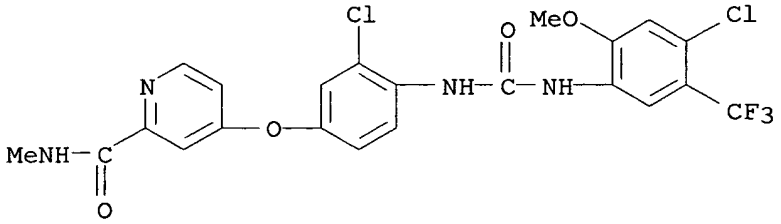


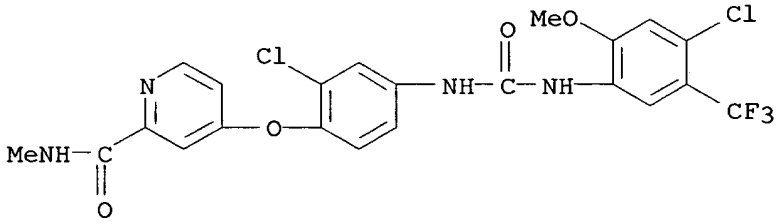
RN 284462-28-8 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-29-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 25 OF 29 USPATFULL on STN
AB This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:171152 USPATFULL
TITLE: Omega-carboxyaryl substituted disphenyl ureas as raf kinase inhibitors
INVENTOR(S): Riedl, Bernd, Wuppertal, Germany, Federal Republic of
Dumas, Jaques, Orange, CT, United States
Khire, Uday, Hamden, CT, United States
Lowinger, Timothy B., Nishinomiya City, Japan
Scott, William J., Guilford, CT, United States

Smith, Roger A., Madison, CT, United States
Wood, Jill E., Hamden, CT, United States
Monahan, Mary-Katherine, Hamden, CT, United States
Natero, Reina, Hamden, CT, United States
Renick, Joel, Milford, CT, United States
Sibley, Robert N., Noth Haven, CT, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001027202	A1	20011004
APPLICATION INFO.:	US 2001-773658	A1	20010202 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-425228, filed on 22 Oct 1999, PENDING Continuation-in-part of Ser. No. US 1999-257266, filed on 25 Feb 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115877P	19990113 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., Arlington Courthouse Plaza I, Suite 1400, 2200 Clarendon Boulevard, Arlington, VA, 22201
NUMBER OF CLAIMS: 67
EXEMPLARY CLAIM: 1
LINE COUNT: 3656
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0003] The p21.sup.ras oncogene is a major contributor to the development and progression of human solid **cancers** and is mutated in 30% of all human **cancers** (Bolton et al. Ann. Rep. Med. Chem. 1994, 29, 165-74; Bos. **Cancer** Res. 1989, 49, 4682-9). In its normal, unmutated form, the ras protein is a key element of the signal transduction. . . . GDP-bound resting form is strictly controlled by ras' endogenous GTPase activity and other regulatory proteins. In the ras mutants in **cancer** cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the **cancerous** growth of the cells which carry these mutants (Magnuson et al. Semin. **Cancer** Biol. 1994, 5, 247-53). It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase. . . . antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human **tumor** types (Monia et al., Nat. Med. 1996, 2, 668-75).

SUMM . . . compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of **tumors** and/or **cancerous** cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal solid **cancers**, e.g., murine **cancer**, since the progression of these **cancers** is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compounds of the invention are useful in treating **cancers**, including solid **cancers**, such as, for example, **carcinomas** (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).

SUMM . . . is directed to compounds which inhibit the enzyme raf kinase and also compounds, compositions and methods for the treatment of **cancerous** cell growth mediated by raf kinase wherein a compound of Formula I is administered or pharmaceutically acceptable salt thereof.

CLM What is claimed is:

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63. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 33.

64. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 38.

65. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 39.

66. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of 3-tert butyl phenyl ureas. . .

67. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of the 3-tert butyl phenyl. . .

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284461-72-9P **284461-73-0P** 284461-74-1P 284461-75-2P
284461-76-3P 284461-77-4P **284461-78-5P** 284461-79-6P
284461-80-9P 284461-81-0P 284461-82-1P **284461-83-2P**
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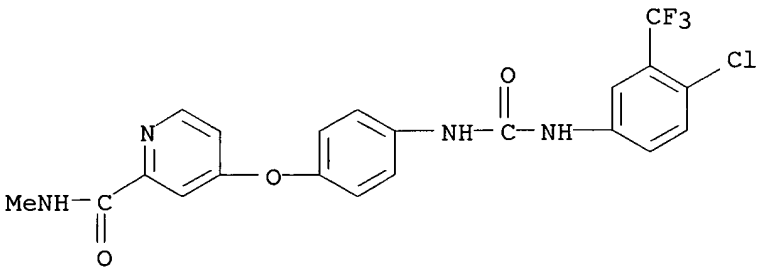
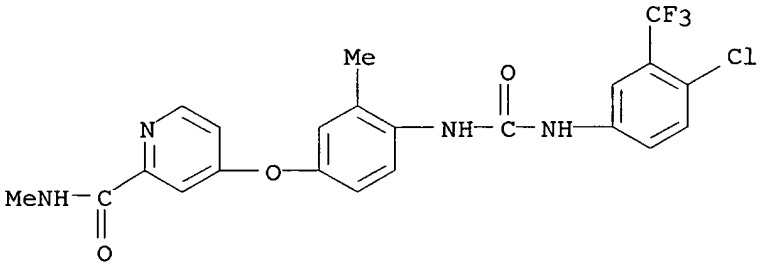
284462-31-3P 284462-32-4P 284462-33-5P 284462-34-6P 284462-35-7P
284462-36-8P 284462-70-0P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

IT **284461-73-0P 284461-78-5P 284461-80-9P**
284461-83-2P 284462-28-8P 284462-29-9P
284462-30-2P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

RN 284461-73-0 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-78-5 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-methylphenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-80-9 USPATFULL
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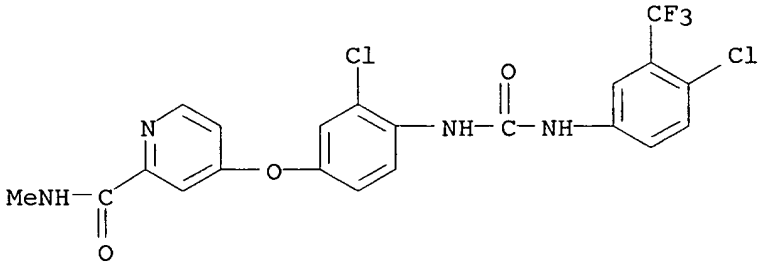
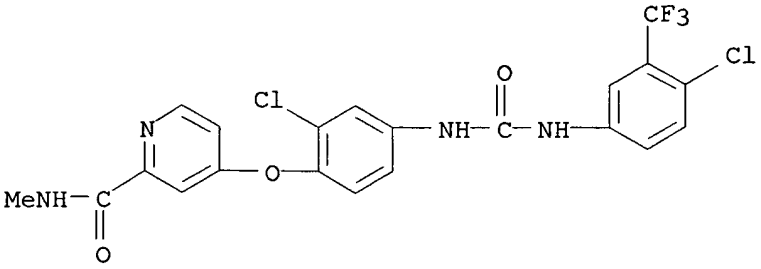
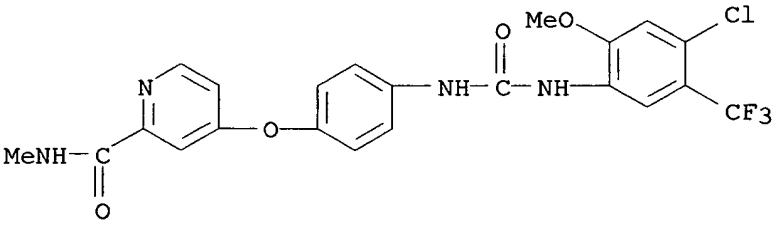


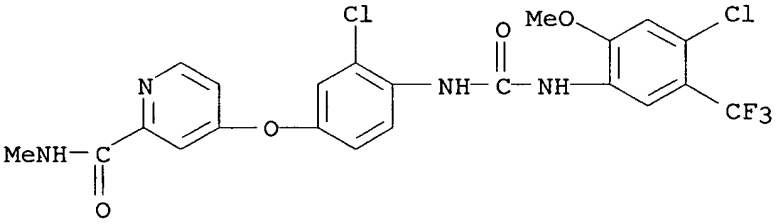
RN 284461-83-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



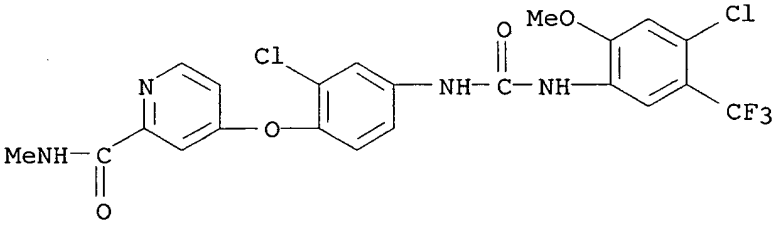
RN 284462-28-8 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-29-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



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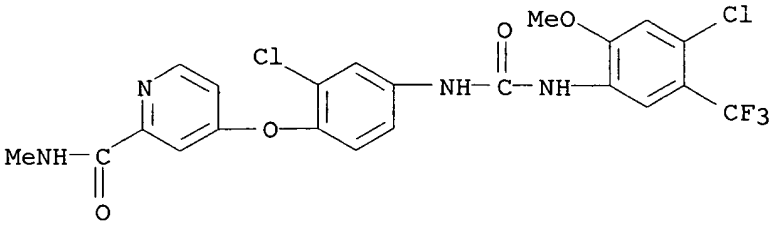

L9 ANSWER 26 OF 29 USPATFULL on STN

AB This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:139616 USPATFULL
TITLE:	Omega-carboxyaryl substituted diphenyl ureas as raf kinase inhibitors
INVENTOR(S):	Riedl, Bernd, Wupperal, Germany, Federal Republic of Dumas, Jacques, Orange, CT, United States Khire, Uday, Hamden, CT, United States Lowinger, Timothy B., Nashnomya City, Japan Scott, William J., Gulford, CT, United States Smith, Roger A., Madison, CT, United States Wood, Jill E., Hamden, CT, United States Monahan, Mary-Katherine, Hamden, CT, United States Natero, Rena, Hamden, CT, United States Renick, Joel, Milford, CT, United States Sibley, Robert N., North Haven, CT, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001016659	A1	20010823
APPLICATION INFO.:	US 2001-773672	A1	20010202 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-425228, filed on 22 Oct 1999, PENDING Continuation-in-part of Ser. No. US 1999-257266, filed on 25 Feb 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115877P	19990113 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS:	67
EXEMPLARY CLAIM:	1
LINE COUNT:	3652

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0003] The p.sub.21ras oncogene is a major contributor to the development and progression of human solid **cancers** and is mutated in 30% of all human **cancers** (Bolton et al. Ann. Rep. Med. Chem. 1994, 29, 165-74; Bos. **Cancer** Res. 1989, 49, 4682-9). In its normal, unmutated form, the ras protein is a key element of the signal transduction. . . GDP-bound resting form is strictly

controlled by ras' endogenous GTPase activity and other regulatory proteins. In the ras mutants in **cancer** cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the **cancerous** growth of the cells which carry these mutants (Magnuson et al. Semin. **Cancer** Biol. 1994, 5, 247-53). It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase. . . antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human **tumor** types (Monia et al., Nat. Med. 1996, 2, 668-75).

SUMM . . . compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of **tumors** and/or **cancerous** cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal solid **cancers**, e.g., murine **cancer**, since the progression of these **cancers** is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compounds of the invention are useful in treating **cancers**, including solid **cancers**, such as, for example, **carcinomas** (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).

SUMM . . . is directed to compounds which inhibit the enzyme raf kinase and also compounds, compositions and methods for the treatment of **cancerous** cell growth mediated by raf kinase wherein a compound of Formula I is administered or pharmaceutically acceptable salt thereof.

CLM What is claimed is:

62. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 1.

63. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 33.

64. A method for the treatment of a **cancerous** cell growth mediated by r af kinase, comprising administering a compound of Formula I of claim 38.

65. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 39.

66. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of 3-tert butyl phenyl ureas. . .

67. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of the 3-tert butyl phenyl. . .

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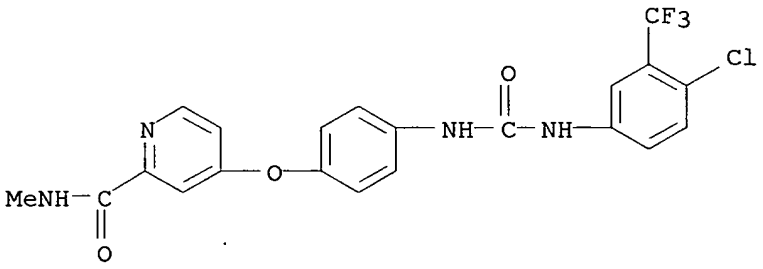
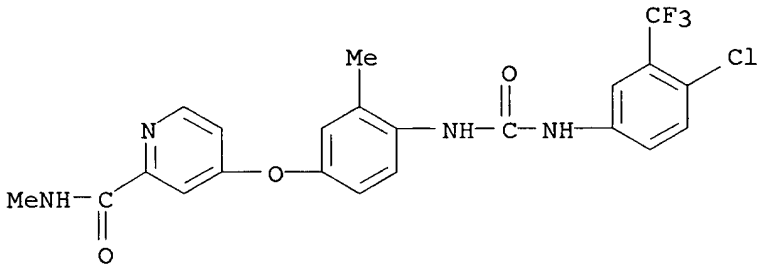
284462-31-3P 284462-32-4P 284462-33-5P 284462-34-6P 284462-35-7P
284462-36-8P 284462-70-0P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

IT **284461-73-0P 284461-78-5P 284461-80-9P**
284461-83-2P 284462-28-8P 284462-29-9P
284462-30-2P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

RN 284461-73-0 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)

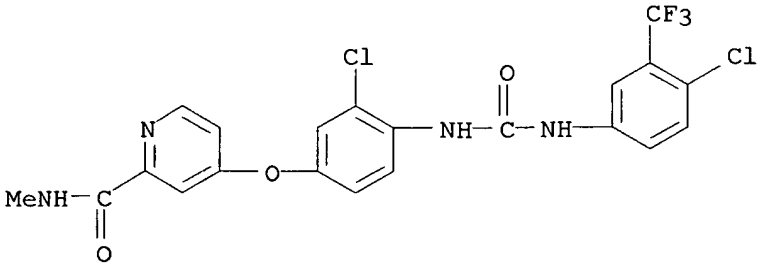


RN 284461-78-5 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-methylphenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-80-9 USPATFULL

CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-83-2 USPATFULL
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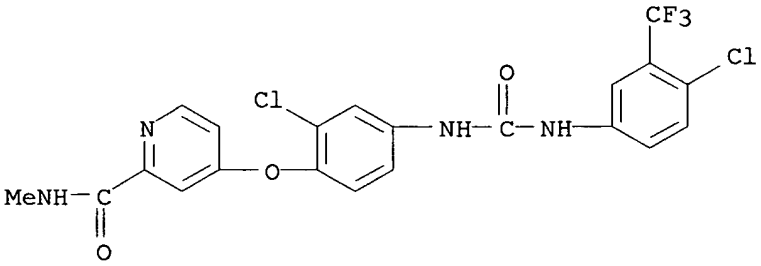
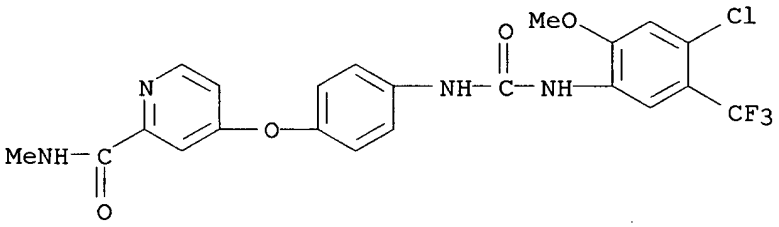
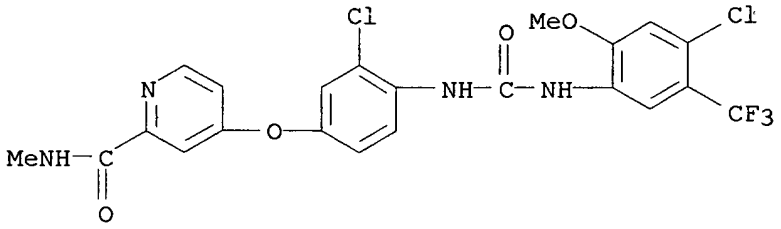


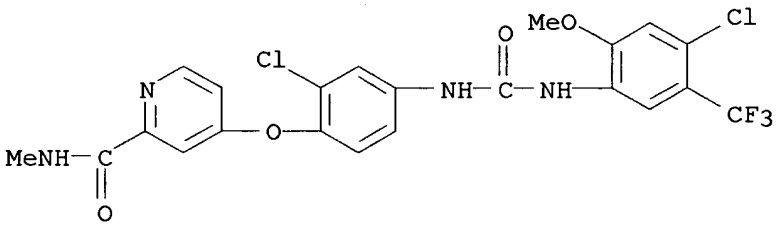
RN 284462-28-8 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-29-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 27 OF 29 USPATFULL on STN
AB This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:123628 USPATFULL
TITLE:	omega-carboxyyaryl substituted diphenyl ureas as raf kinase inhibitors
INVENTOR(S):	Riedl, Bernd, Wuppertal, Germany, Federal Republic of Dumas, Jacques, Orange, CT, United States Khire, Uday, Hamden, CT, United States Lowinger, Timothy B., Nishinomiya City, Japan Scott, William J., Guilford, CT, United States Smith, Roger A., Madison, CT, United States Wood, Jill E., Hamden, CT, United States Monahan, Mary-Katherine, Hamden, CT, United States Natero, Reina, Hamden, CT, United States Renick, Joel, Milford, CT, United States Sibley, Robert N., North Haven, CT, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001011136	A1	20010802
APPLICATION INFO.:	US 2001-773675	A1	20010202 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-425228, filed on 22 Oct 1999, PENDING Continuation-in-part of Ser. No. US 1999-257266, filed on 25 Feb 1999, ABANDONED

	NUMBER	DATE

PRIORITY INFORMATION:	US 1999-115877P 19990113 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MILLEN, WHITE, ZELANO & BRANIGAN, P.C., Suite 1400, 2200 Clarendon Blvd., Arlington, VA, 22201
NUMBER OF CLAIMS:	67
EXEMPLARY CLAIM:	1
LINE COUNT:	3646

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0003] The p21.sup.ras oncogene is a major contributor to the development and progression of human solid **cancers** and is mutated in 30% of all human **cancers** (Bolton et al. Ann. Rep. Med. Chem. 1994, 29, 165-74; Bos. **Cancer** Res. 1989, 49, 4682-9). In its normal, unmutated form, the ras protein is a key element of the signal transduction. . . . GDP-bound resting form is strictly controlled by ras' endogenous GTPase activity and other regulatory proteins. In the ras mutants in **cancer** cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the **cancerous** growth of the cells which carry these mutants (Magnuson et al. Semin. **Cancer** Biol. 1994, 5, 247-53). It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase. . . . antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human **tumor** types (Monia et al., Nat. Med. 1996, 2, 668-75).

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SUMM . . . is directed to compounds which inhibit the enzyme raf kinase and also compounds, compositions and methods for the treatment of **cancerous** cell growth mediated by raf kinase wherein a compound of Formula I is administered or pharmaceutically acceptable salt thereof.

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63. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 33.

64. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 38.

65. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 39.

66. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of 3-tert butyl phenyl ureas. . .

67. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of the 3-tert butyl phenyl. . .

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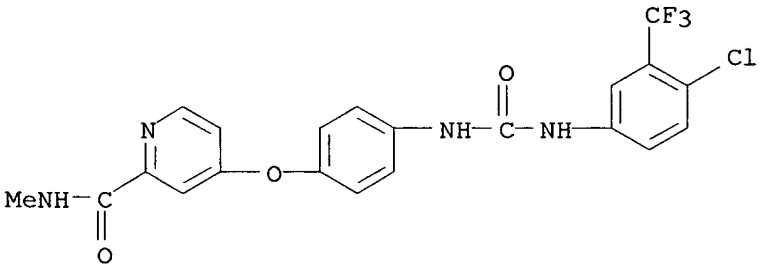
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

IT **284461-73-0P 284461-78-5P 284461-80-9P**
284461-83-2P 284462-28-8P 284462-29-9P
284462-30-2P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

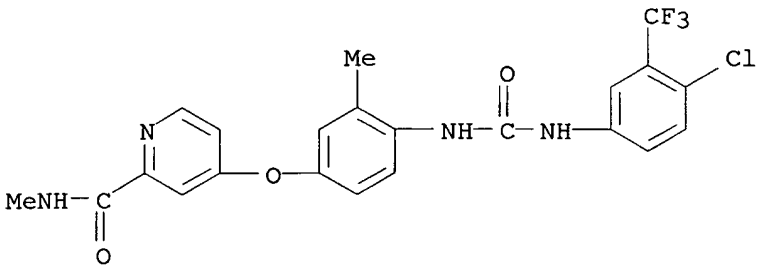
RN 284461-73-0 USPATFULL

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)

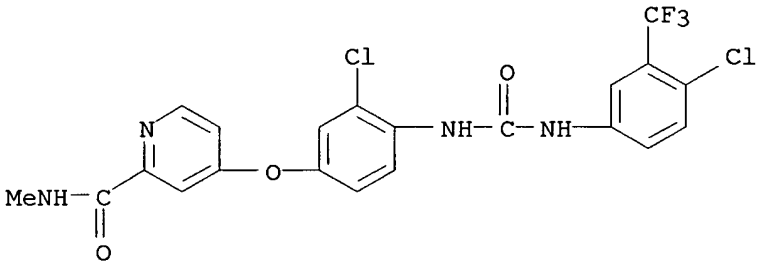


RN 284461-78-5 USPATFULL

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-methylphenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-80-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-83-2 USPATFULL
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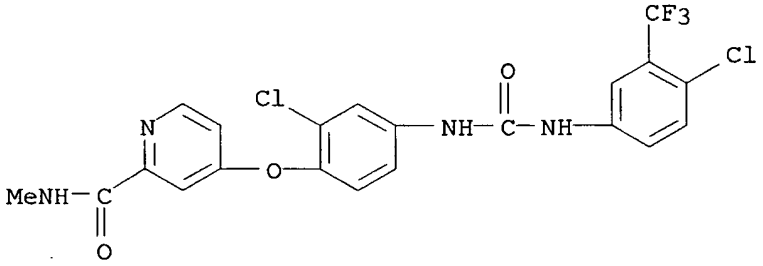

RN 284462-28-8 USPATFULL
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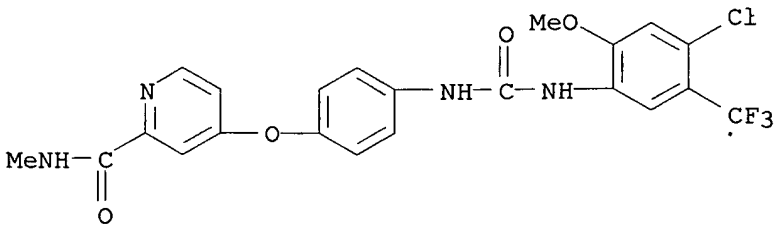
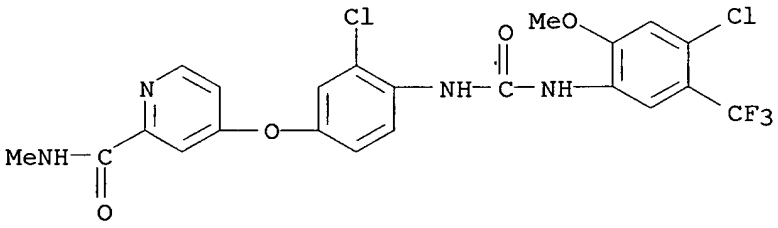
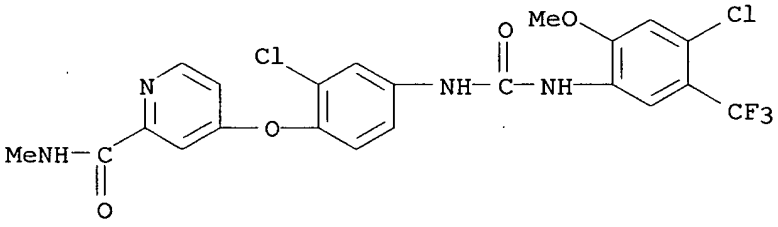


RN 284462-29-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 28 OF 29 USPATFULL on STN
AB This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:123627 USPATFULL
TITLE: Omega-carboxyaryl subsituted diphenyl ureas as raf kinase inhibitors
INVENTOR(S): Riedl, Bernd, Wuppertal, Germany, Federal Republic of
Dumas, Jacques, Orange, CT, United States
Khire, Uday, Hamden, CT, United States
Lowinger, Timothy B., Nishinomiya City, Japan
Scott, William J., Guilford, CT, United States

Smith, Roger A., Madison, CT, United States
Wood, Jill E., Hamden, CT, United States
Monahan, Mary-Katherine, Hamden, CT, United States
Natero, Reina, Hamden, CT, United States
Renick, Joel, Milford, CT, United States
Sibley, Robert N., North Haven, CT, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001011135	A1	20010802
APPLICATION INFO.:	US 2001-773659	A1	20010202 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-425228, filed on 22 Oct 1999, PENDING Continuation-in-part of Ser. No. US 1999-257266, filed on 25 Feb 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115877P	19990113 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., Suite 1400, Arlington Courthouse Plaza 1, Arlington, VA, 22201
NUMBER OF CLAIMS: 67
EXEMPLARY CLAIM: 1
LINE COUNT: 3686
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0003] The p21.sup.ras oncogene is a major contributor to the development and progression of human solid **cancers** and is mutated in 30% of all human **cancers** (Bolton et al. Ann. Rep. Med. Chem. 1994, 29, 165-74; Bos. **Cancer** Res. 1989, 49, 4682-9). In its normal, unmutated form, the ras protein is a key element of the signal transduction. . . . GDP-bound resting form is strictly controlled by ras' endogenous GTPase activity and other regulatory proteins. In the ras mutants in **cancer** cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the **cancerous** growth of the cells which carry these mutants (Magnuson et al. Semin. **Cancer** Biol. 1994, 5, 247-53). It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase. . . . antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human **tumor** types (Monia et al., Nat. Med. 1996, 2, 668-75).

SUMM . . . compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of **tumors** and/or **cancerous** cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal solid **cancers**, e.g., murine **cancer**, since the progression of these **cancers** is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compounds of the invention are useful in treating **cancers**, including solid **cancers**, such as, for example, **carcinomas** (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).

SUMM . . . is directed to compounds which inhibit the enzyme raf kinase

and also compounds, compositions and methods for the treatment of **cancerous** cell growth mediated by raf kinase wherein a compound of Formula I is administered or pharmaceutically acceptable salt thereof.

CLM What is claimed is:

62. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 1.

63. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 33.

64. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 38.

65. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administering a compound of Formula I of claim 39.

66. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of 3-tert butyl phenyl ureas. . .

67. A method for the treatment of a **cancerous** cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of the 3-tert butyl phenyl. . .

IT 228418-48-2P 284461-33-2P 284461-34-3P 284461-35-4P 284461-36-5P
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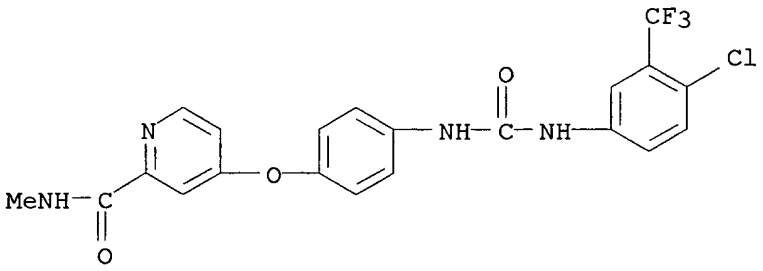
284462-24-4P 284462-25-5P 284462-26-6P 284462-27-7P
284462-28-8P 284462-29-9P 284462-30-2P
284462-31-3P 284462-32-4P 284462-33-5P 284462-34-6P 284462-35-7P
284462-36-8P 284462-70-0P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

IT **284461-73-0P 284461-78-5P 284461-80-9P**
284461-83-2P 284462-28-8P 284462-29-9P
284462-30-2P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

RN 284461-73-0 USPATFULL

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-78-5 USPATFULL
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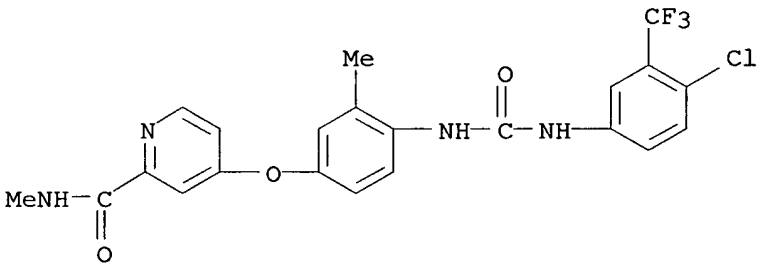
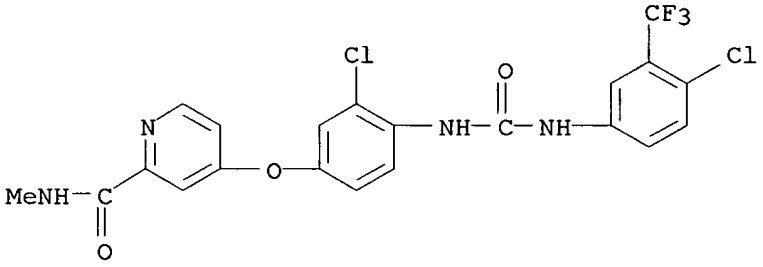
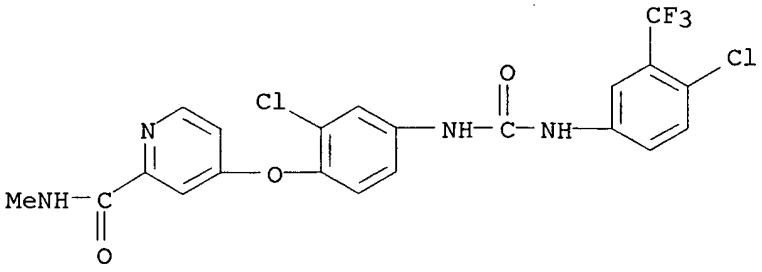


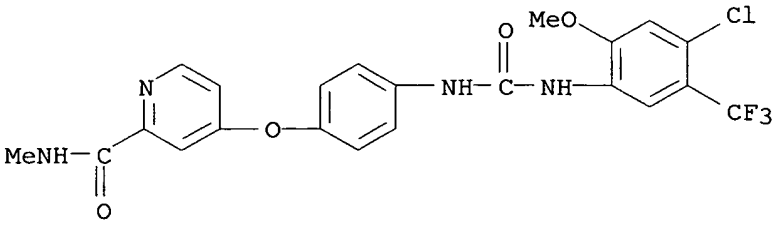
RN 284461-80-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



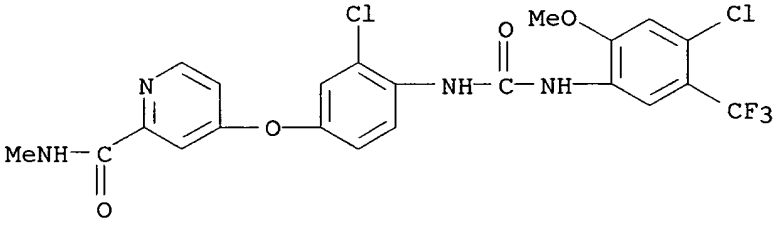
RN 284461-83-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



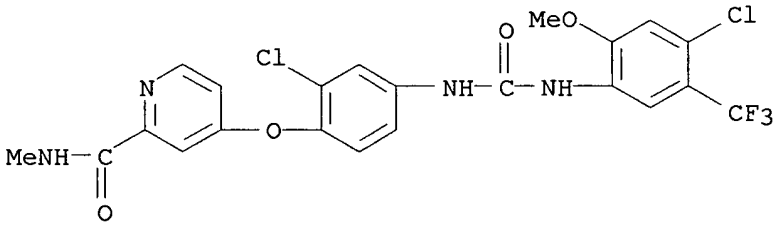
RN 284462-28-8 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-29-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



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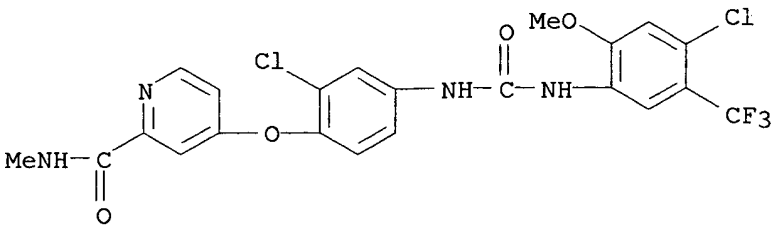

L9 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
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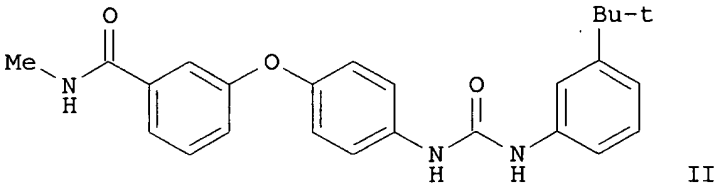

II

AB This invention relates to the prepn. and use of (hetero)aryl ureas ANHCONHB [I; A = L(ML1)q; L = 5- or 6-membered (hetero)aryl, esp. Ph or pyridinyl; M = bridging group; L1 = (hetero)aryl with at least one (un)substituted sulfamoyl, carboxy, or carbamoyl substituent; q = 1-3; B = certain (un)substituted mono- to tricyclic aryl or heteroaryl groups] for the treatment of raf mediated diseases, such as **cancer** (no data). Approx. 100 invention compds. and numerous intermediates were prepd. For instance, 3-tert-butylaniline was coupled with bis(trichloromethyl)carbonate to form the isocyanate, followed by addn. of 4-(3-N-methylcarbamoylphenoxy)aniline (prepn. given) to afford the urea II.

ACCESSION NUMBER: 2000:493516 HCAPLUS
DOCUMENT NUMBER: 133:120157
TITLE: Preparation of .omega.-carboxy(hetero)aryl substituted diphenyl ureas as raf kinase inhibitors
INVENTOR(S): Riedl, Bernd; Dumas, Jacques; Khire, Uday; Lowinger, Timothy B.; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Monahan, Mary-Katherine; Natero, Reina; Renick, Joel; Sibley, Robert N.
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000042012	A1	20000720	WO 2000-US648	20000112

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,

IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2359510	AA	20000720	CA 2000-2359510	20000112	
EP 1140840	A1	20011010	EP 2000-903239	20000112	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
EE 200100368	A	20030415	EE 2001-368	20000112	
JP 2003526613	T2	20030909	JP 2000-593580	20000112	
BR 2000007487	A	20030923	BR 2000-7487	20000112	
US 2001011135	A1	20010802	US 2001-773659	20010202	
US 2001011136	A1	20010802	US 2001-773675	20010202	
US 2001016659	A1	20010823	US 2001-773672	20010202	
US 2001027202	A1	20011004	US 2001-773658	20010202	
US 2001034447	A1	20011025	US 2001-773604	20010202	
NO 2001003463	A	20010912	NO 2001-3463	20010712	
US 2002137774	A1	20020926	US 2001-907970	20010719	
BG 105763	A	20020329	BG 2001-105763	20010801	
HR 2001000580	A1	20020831	HR 2001-580	20010802	
US 2002042517	A1	20020411	US 2001-948915	20010910	
US 2003139605	A1	20030724	US 2002-71248	20020211	

PRIORITY APPLN. INFO.:	US 1999-115877P	P	19990113
	US 1999-257266	A2	19990225
	US 1999-425228	A2	19991022
	US 1999-115878P	P	19990113
	WO 2000-US648	W	20000112
	US 2001-948915	A1	20010910

OTHER SOURCE(S): MARPAT 133:120157

AB . . . B = certain (un)substituted mono- to tricyclic aryl or heteroaryl groups] for the treatment of raf mediated diseases, such as **cancer** (no data). Approx. 100 invention compds. and numerous intermediates were prepd. For instance, 3-tert-butylaniline was coupled with bis(trichloromethyl)carbonate to form. . .

IT 284461-33-2P, N-(3-tert-Butylphenyl)-N'-(4-(3-(N-methylcarbamoyl)phenoxy)phenyl)urea 284461-34-3P, N-(3-tert-Butylphenyl)-N'-(4-(4-acetylphenoxy)phenyl)urea 284461-36-5P, N-(5-tert-Butyl-2-methoxyphenyl)-N'-[4-[3-(N-methylcarbamoyl)phenoxy]phenyl]urea 284461-37-6P, N-(5-tert-Butyl-2-methoxyphenyl)-N'-[4-[4-methoxy-3-(N-methylcarbamoyl)phenoxy]phenyl]urea 284461-39-8P, N-(5-tert-Butyl-2-methoxyphenyl)-N'-[4-(1-oxoisoindolin-5-yloxy)phenyl]urea 284461-42-3P 284461-43-4P, N-[2-Methoxy-5-(trifluoromethyl)phenyl]-N'-[3-(2-carbamoyl-4-pyridyloxy)phenyl]urea 284461-44-5P 284461-45-6P, N-[2-Methoxy-5-(trifluoromethyl)phenyl]-N'-[4-(2-carbamoyl-4-pyridyloxy)phenyl]urea 284461-51-4P 284461-54-7P 284461-58-1P, N-[2-Methoxy-5-(trifluoromethyl)phenyl]-N'-[4-[[2-(N-methylcarbamoyl)-4-pyridyl]thio]phenyl]urea 284461-74-1P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-(2-carbamoyl-4-pyridyloxy)phenyl]urea 284461-75-2P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[3-(2-carbamoyl-4-pyridyloxy)phenyl]urea **284461-78-5P** 284461-86-5P 284461-90-1P 284461-99-0P 284462-05-1P 284462-06-2P 284462-17-5P 284462-18-6P 284462-19-7P, N-[4-Bromo-3-(trifluoromethyl)phenyl]-N'-[2-chloro-4-[[2-(N-methylcarbamoyl)-4-pyridyl]oxy]phenyl]urea 284462-20-0P, N-[4-Bromo-3-(trifluoromethyl)phenyl]-N'-[3-chloro-4-[[2-(N-

methylcarbamoyl)-4-pyridyl]oxy]phenyl]urea 284462-22-2P, N-[4-Bromo-3-(trifluoromethyl)phenyl]-N'-[3-[[2-(N-methylcarbamoyl)-4-pyridyl]oxy]phenyl]urea 284462-26-6P **284462-28-8P**, N-[2-Methoxy-4-chloro-5-(trifluoromethyl)phenyl]-N'-[4-[[2-(N-methylcarbamoyl)-4-pyridyl]oxy]phenyl]urea **284462-30-2P** 284462-31-3P, N-[2-Methoxy-4-chloro-5-(trifluoromethyl)phenyl]-N'-[3-[[2-(N-methylcarbamoyl)-4-pyridyl]oxy]phenyl]urea 284462-35-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of .omega.-carboxy(hetero)aryl substituted di-Ph urea raf kinase inhibitors by reacting arylisocyanates with arylamines)

IT 228418-48-2P 284461-35-4P 284461-40-1P 284461-41-2P 284461-46-7P
284461-47-8P 284461-49-0P 284461-50-3P 284461-52-5P 284461-53-6P
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284462-32-4P 284462-33-5P 284462-34-6P 284462-36-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of .omega.-carboxy(hetero)aryl substituted di-Ph urea raf kinase inhibitors by reacting arylisocyanates with arylamines)

IT 98-98-6, Picolinic acid 99-98-9, 4-(Dimethylamino)aniline 106-50-3, p-Phenylenediamine, reactions 108-00-9, N,N-Dimethylethylenediamine 109-85-3, 2-Methoxyethylamine 110-13-4, Acetonylacetone 123-30-8, 4-Aminophenol 320-51-4, 4-Chloro-3-(trifluoromethyl)aniline 327-78-6, 4-Chloro-3-(trifluoromethyl)phenyl isocyanate 349-65-5, 2-Methoxy-5-(trifluoromethyl)aniline 350-46-9, 1-Fluoro-4-nitrobenzene 371-40-4, 4-Fluoroaniline 393-36-2, 4-Bromo-3-(trifluoromethyl)aniline 462-08-8, 3-Aminopyridine 610-35-5, 4-Hydroxyphthalic acid 619-08-9, 2-Chloro-4-nitrophenol 626-61-9, 4-Chloropyridine 883-99-8, Methyl 3-hydroxy-2-naphthoate 1121-78-4, 5-Hydroxy-2-methylpyridine 1215-98-1, 4-(4-Acetylphenoxy)aniline 1664-40-0, N-Phenylethylenediamine 1877-71-0, Monomethyl isophthalate 2038-03-1, 4-(2-Aminoethyl)morpholine 2252-63-3, N-(4-Fluorophenyl)piperazine 2524-67-6, 4-Morpholinoaniline 2835-99-6, 4-Amino-3-methylphenol 2905-24-0, 3-Bromobenzenesulfonyl chloride 5369-19-7, 3-tert-Butylaniline 6310-19-6, 2-Nitro-4-tert-butylaniline 6628-77-9, 5-Amino-2-methoxypyridine 6927-86-2, 4-(4-Acetylphenoxy)aniline hydrochloride 7781-98-8, Ethyl 3-hydroxybenzoate 13154-24-0, Triisopropylsilyl chloride 16588-75-3 25900-61-2, 3-(Methylcarbamoyl)aniline 29264-35-5, 4-(3-Carboxy-4-hydroxyphenoxy)-1-nitrobenzene 30766-22-4, Methyl 5-hydroxynicotinate 30806-83-8, Ethyl 4-isocyanatobenzoate 34803-66-2, N-(2-Pyridyl)piperazine 36265-31-3, 4-(4-Methylthiophenoxy)-1-nitrobenzene 51639-48-6, N-(4-Acetylphenyl)piperazine 73441-86-8 150009-83-9, 3-Amino-2-methoxyquinoline 284461-38-7, N-(5-tert-Butyl-2-methoxyphenyl)-N'-[4-(1,3-dioxoisoindolin-5-yloxy)phenyl]urea 284461-48-9

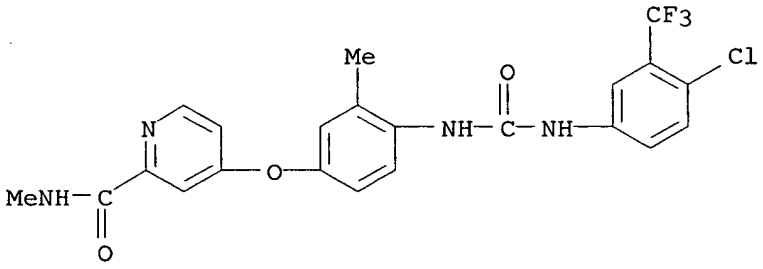
284461-76-3, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-(3-((2-(N-Methylcarbamoyl)-4-pyridyl)oxy)phenyl)urea **284462-29-9**
284462-72-2, 3-Chloro-6-(N-acetylamino)-4-(trifluoromethyl)anisole
284462-73-3, 4-Chloro-N-(2-hydroxyethyl)pyridine-2-carboxamide
284462-74-4 284462-76-6 284462-77-7, 5-tert-Butyl-2-methoxyphenyl isocyanate 284462-78-8, 3-[[2-(N-Methylcarbamoyl)-4-pyridyl]oxy]aniline
284462-79-9, 3-(2-Carbamoyl-4-pyridyloxy)aniline 284462-80-2, 4-(2-Carbamoyl-4-pyridyloxy)aniline 284462-82-4, 4-[[2-(N-Ethylcarbamoyl)-4-pyridyl]oxy]aniline 284462-83-5, 4-[[2-(N-Methylcarbamoyl)-4-pyridyl]oxy]-3-chloroaniline 284462-85-7, 4-(3-Carbamoylphenoxy)aniline 284462-86-8, 4-[[2-(N,N-Dimethylcarbamoyl)-4-pyridyl]oxy]aniline 284462-87-9 284462-88-0 284462-89-1, 4-[[2-(N-Isopropylcarbamoyl)-4-pyridyl]oxy]aniline 284462-92-6, 3-[[2-(N-Methylcarbamoyl)-4-pyridyl]oxy]-4-methylaniline 284462-93-7, 4-[3-[N-(2-Morpholinylethyl)carbamoyl]phenoxy]aniline 284462-94-8, 4-[3-[N-(2-Piperidylethyl)carbamoyl]phenoxy]aniline 284462-95-9, 4-[3-[N-(Tetrahydrofurylmethyl)carbamoyl]phenoxy]aniline 284462-96-0
284462-99-3, 4-Chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate
284670-99-1, 4-(4-Acetylphenoxy)-5-aminopyridine 284671-00-7, N-[5-(Trifluoromethyl)-2-methoxyphenyl]-N'-[4-[3-(5-methoxycarbonylpyridyl)oxy]phenyl]urea 284671-01-8, N-[5-(Trifluoromethyl)-2-methoxyphenyl]-N'-(3-carboxyphenyl)urea
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of .omega.-carboxy(hetero)aryl substituted di-Ph urea raf kinase inhibitors by reacting arylisocyanates with arylamines)

IT 883-62-5P, 3-Methoxy-2-naphthoic acid 13041-60-6P, Methyl 3-methoxy-2-naphthoate 27237-21-4P, 4-(3-Carboxyphenoxy)-1-nitrobenzene 36089-89-1P, 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene 41513-02-4P, 4-Bromo-3-(trifluoromethyl)phenyl isocyanate 50727-06-5P, 5-Hydroxyisoindoline-1,3-dione 51727-15-2P, 4-Chloropyridine-2-carbonyl chloride hydrochloride 54579-63-4P, 4-(3-Carboxyphenoxy)aniline 64064-63-7P, 4-[(2-Methylpyridin-5-yl)oxy]-1-nitrobenzene 67291-63-8P, 2-Amino-3-methoxynaphthalene 71708-64-0P, 4-[3-(N-Methylcarbamoyl)phenoxy]-1-nitrobenzene 77992-50-8P, 4-Bromo-3-(trifluoromethyl)aniline hydrochloride 119431-22-0P, 3-Chloro-4-(2,2,2-trifluoroacetylamino)phenol 153435-79-1P, N-Methyl-3-bromobenzenesulfonamide 176977-85-8P, Methyl 4-chloropyridine-2-carboxylate hydrochloride 220000-87-3P, 4-Chloro-N-methyl-2-pyridinecarboxamide 228401-15-8P, 2-(N-(Benzyloxycarbonyl)amino)-3-methoxynaphthalene 228401-43-2P, 4-(3-Methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene 228401-44-3P, 4-(3-Carboxy-4-methoxyphenoxy)-1-nitrobenzene 252061-66-8P, 5-Hydroxyisoindolin-1-one **284461-73-0P** 284461-89-8P
284462-37-9P, 4-[[2-(N-Methylcarbamoyl)-4-pyridyl]oxy]aniline
284462-38-0P, 5-(4-Nitrophenoxy)isoindoline-1,3-dione 284462-39-1P, 5-(4-Aminophenoxy)isoindoline-1,3-dione 284462-40-4P, 1-(4-tert-Butyl-2-nitrophenyl)-2,5-dimethylpyrrole 284462-41-5P, 5-tert-Butyl-2-(2,5-dimethylpyrrolyl)aniline 284462-42-6P, 4-[[2-(N-Methylcarbamoyl)-4-pyridyl]oxy]-2-methylaniline hydrochloride 284462-43-7P 284462-44-8P 284462-45-9P, 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline 284462-46-0P, 4-[3-(N-Methylcarbamoyl)-4-methoxyphenoxy]-1-nitrobenzene 284462-47-1P, 4-[3-(N-Methylcarbamoyl)-4-methoxyphenoxy]aniline 284462-48-2P, 5-(4-Nitrophenoxy)-2-methylisoindoline-1,3-dione 284462-49-3P, 5-(4-Aminophenoxy)-2-methylisoindoline-1,3-dione 284462-51-7P, 4-Chloro-2-[N-(2-morpholin-4-ylethyl)carbamoyl]pyridine 284462-52-8P 284462-53-9P, 4-(1-Oxoisoindolin-5-yloxy)-1-nitrobenzene 284462-54-0P,

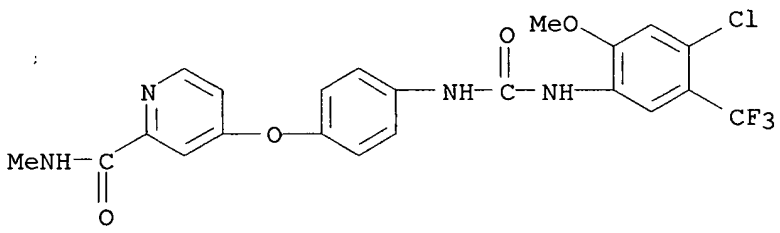
4-(1-Oxoisoindolin-5-yloxy)aniline 284462-55-1P, 4-(3-Ethoxycarbonylphenoxy)-1-nitrobenzene 284462-56-2P, 4-[3-(N-Methylcarbamoyl)phenoxy]aniline 284462-57-3P 284462-58-4P 284462-59-5P 284462-60-8P, 4-[3-(N-Methylsulfamoyl)phenoxy]-1-nitrobenzene 284462-61-9P, 4-[3-(N-Methylsulfamoyl)phenoxy]aniline 284462-62-0P 284462-63-1P, 4-Chloro-N-[2-(triisopropylsilyloxy)ethyl]pyridine-2-carboxamide 284462-64-2P 284462-65-3P, 4-[[2-(Methoxycarbonyl)pyridin-5-yl]oxy]-1-nitrobenzene 284462-66-4P 284462-67-5P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'(4-aminophenyl)Urea 284462-68-6P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'(4-ethoxycarbonylphenyl)Urea 284462-69-7P 284462-70-0P 284462-71-1P 284462-84-6P, 4-(4-Methylsulfonylphenoxy)-1-aniline 284462-97-1P 284670-98-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of .omega.-carboxy(hetero)aryl substituted di-Ph urea raf kinase inhibitors by reacting arylisocyanates with arylamines)

IT **284461-78-5P 284462-28-8P,** N-[2-Methoxy-4-chloro-5-(trifluoromethyl)phenyl]-N'-[4-[[2-(N-methylcarbamoyl)-4-pyridyl]oxy]phenyl]urea **284462-30-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of .omega.-carboxy(hetero)aryl substituted di-Ph urea raf kinase inhibitors by reacting arylisocyanates with arylamines)

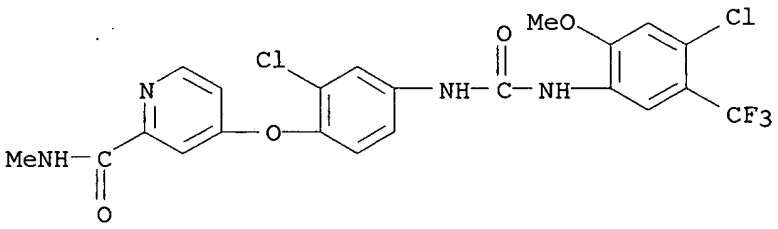
RN 284461-78-5 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-methylphenoxy]-N-methyl- (9CI) (CA INDEX NAME)



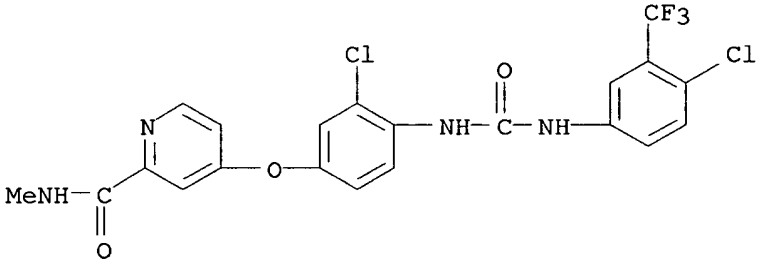
RN 284462-28-8 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



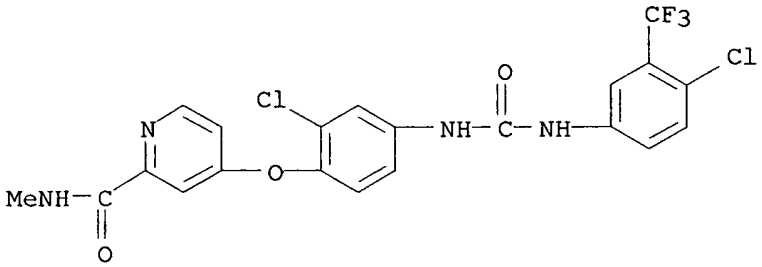
RN 284462-30-2 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



IT **284461-80-9P 284461-83-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of .omega.-carboxy(hetero)aryl substituted di-Ph urea raf kinase inhibitors by reacting arylisocyanates with arylamines)
RN 284461-80-9 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-83-2 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



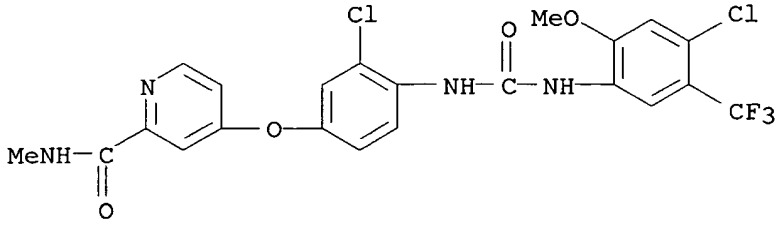
IT **284462-29-9**

DELACROIX

RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of .omega.-carboxy(hetero)aryl substituted di-Ph urea raf kinase inhibitors by reacting arylisocyanates with arylamines)

RN 284462-29-9 HCAPLUS

CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)

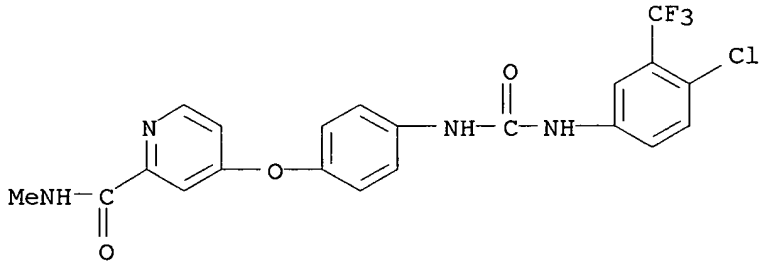


IT **284461-73-0P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of .omega.-carboxy(hetero)aryl substituted di-Ph urea raf kinase inhibitors by reacting arylisocyanates with arylamines)

RN 284461-73-0 HCAPLUS

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

FILE 'HCAPLUS' ENTERED AT 20:58:23 ON 22 JAN 2004

FILE 'USPATFULL' ENTERED AT 20:58:23 ON 22 JAN 2004

=> d his

(FILE 'HOME' ENTERED AT 20:56:48 ON 22 JAN 2004)

FILE 'REGISTRY' ENTERED AT 20:57:10 ON 22 JAN 2004
L1 STRUCTURE UPLOADED
L2 1 S L1 SSS SAM
L3 9 S L1 SSS FULL

FILE 'HCAPLUS, USPATFULL' ENTERED AT 20:58:23 ON 22 JAN 2004

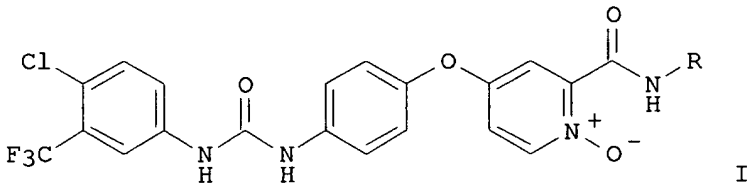
=> s l3
L4 40 L3

=> s l4 and arthrit?
L5 6 L4 AND ARTHRIT?

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6 6 DUP REM L5 (0 DUPLICATES REMOVED)

=> d l6 abs ibib kwic hitstr 1-6

L6 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
GI



I

AB The title ureas contg. a pyridine, quinoline, or isoquinoline functionality which is oxidized at the nitrogen heteroatom MLBNHCONHA [A = (un)substituted Ph, naphthyl, 5-6 membered monocyclic heteroaryl, 8-10 membered bicyclic heteroaryl; B = (un)substituted phenylene, naphthylene, 5-6 membered monocyclic heteroarylene, 8-10 membered bicyclic heteroarylene; L = (CH2)mO(CH2)l, (CH2)m(CH2)l, (CH2)mCO(CH2)l, etc.; m, l = 0-4; M = (un)substituted pyridine-1-oxide, quinoline-1-oxide, isoquinoline-1-oxide; with the provisos] which are useful in the treatment of (i) raf mediated diseases, for example, cancer, (ii) p38 mediated

diseases such as inflammation and osteoporosis, and (iii) VEGF mediated diseases such as angiogenesis disorders, were claimed. Prepn. of two ureas such as I [R = H, Me] which are not compds. of the invention, and have been distinguished from the compds. of the invention by a proviso, was described. Pharmaceutical compn. comprising the title ureas was claimed.

ACCESSION NUMBER: 2003:656581 HCAPLUS
DOCUMENT NUMBER: 139:197370
TITLE: Preparation of aryl ureas containing pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors
INVENTOR(S): Dumas, Jacques; Scott, William J.; Riedl, Bernd
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068229	A1	20030821	WO 2003-US4110	20030211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003216396	A1	20031120	US 2003-361850	20030211

PRIORITY APPLN. INFO.: US 2002-354935P P 20020211
OTHER SOURCE(S): MARPAT 139:197370

IT **Arthritis**
Shock (circulatory collapse)
(septic, treatment of; prepn. of aryl ureas contg. pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors)

IT Alzheimer's disease
Asthma
Atherosclerosis
Inflammation
Lymphoma
Multiple sclerosis
Myelodysplastic syndromes
Osteoarthritis
Osteoporosis
Periodontium, disease
Psoriasis
Rheumatic fever
Rheumatoid **arthritis**
Sepsis
Silicosis
Tuberculosis

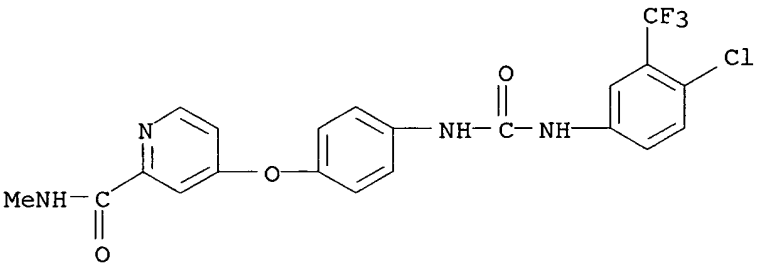
(treatment of; prepn. of aryl ureas contg. pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors)

IT 123-30-8, 4-Aminophenol 320-51-4 176977-85-8, Methyl 4-chloro-2-pyridinecarboxylate hydrochloride **284461-73-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of aryl ureas contg. pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors)

IT **583840-03-3P** 583840-04-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of aryl ureas contg. pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors)

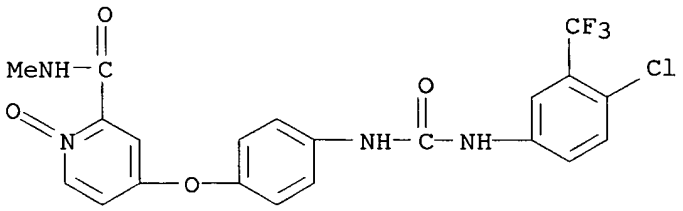
IT **284461-73-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of aryl ureas contg. pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors)

RN 284461-73-0 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



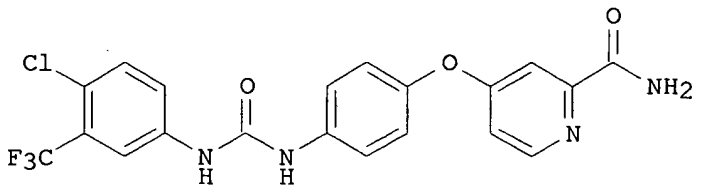
IT **583840-03-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of aryl ureas contg. pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors)

RN 583840-03-3 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-, 1-oxide (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
GI



I

AB The title compds. ANHCONHB [A, B = (un)substituted Ph, naphthyl, 5-6 membered monocyclic heteroaryl, etc.], useful for treating diseases mediated by the VEGF induced signal transduction pathway characterized by abnormal angiogenesis or hyperpermeability processes, were claimed. Prepns. of three title ureas are described. E.g., a 3-step synthesis of the urea I (starting from Me 4-chloro-2-pyridinecarboxylate hydrochloride), was given. The KDR (VEGFR2) assay for testing the title ureas is described.

ACCESSION NUMBER: 2003:656580 HCAPLUS
DOCUMENT NUMBER: 139:197369
TITLE: Preparation of aryl ureas with angiogenesis inhibiting activity
INVENTOR(S): Dumas, Jacques; Scott, William J.; Elting, James; Hatoum-Makdad, Holia
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068228	A1	20030821	WO 2003-US4103	20030211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003207870	A1	20031106	US 2003-361858	20030211

PRIORITY APPLN. INFO.: US 2002-354950P P 20020211
OTHER SOURCE(S): MARPAT 139:197369

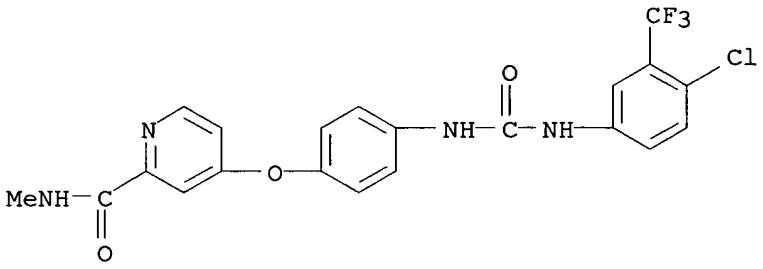
IT Alzheimer's disease
Asthma
Atherosclerosis
Lymphoma
Multiple sclerosis
Myelodysplastic syndromes
Psoriasis
Rheumatic fever
Rheumatoid **arthritis**

Sepsis
Silicosis
Tuberculosis
(treatment of; prepn. of aryl ureas with angiogenesis inhibiting activity)

IT 284461-44-5P **284461-73-0P** 284461-74-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aryl ureas with angiogenesis inhibiting activity)

IT **284461-73-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aryl ureas with angiogenesis inhibiting activity)

RN 284461-73-0 HCAPLUS
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 6 USPATFULL on STN

AB This invention relates to new aryl ureas and methods for their synthesis. The inventive compounds are useful in the treatment of (i) raf mediated diseases, for example, cancer, (ii) p38 mediated diseases such as inflammation and osteoporosis, and (iii) VEGF mediated diseases such as angiogenesis disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:307010 USPATFULL
TITLE: Aryl ureas as kinase inhibitors
INVENTOR(S): Dumas, Jacques, Orange, CT, UNITED STATES
Scott, William J., Guilford, CT, UNITED STATES
Riedl, Bernd, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Chien, Du-Shieng, Guilford, CT, UNITED STATES
Nassar, Ala, Milford, CT, UNITED STATES
Lee, Wendy, Hamden, CT, UNITED STATES
Bjorge, Susan, Milford, CT, UNITED STATES
Musza, Laszlo L., Guilford, CT, UNITED STATES
PATENT ASSIGNEE(S): BAYER CORPORATION, Pittsburgh, PA, UNITED STATES (U.S. corporation)

NUMBER	KIND	DATE

PATENT INFORMATION: US 2003216446 A1 20031120
APPLICATION INFO.: US 2003-361859 A1 20030211 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-354937P	20020211 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS: 73
EXEMPLARY CLAIM: 1
LINE COUNT: 1856
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0007] Clinical studies have linked TNF.alpha. production and/or signaling to a number of diseases including rheumatoid **arthritis** (Maini. J. Royal Coll. Physicians London 1996, 30, 344). In addition, excessive levels of TNF.alpha. have been implicated in a. . . 1996, 149, 195), myelodysplastic syndromes (Raza et al. Int. J. Hematol. 1996, 63, 265), systemic lupus erythematosus (Maury et al. **Arthritis** Rheum. 1989, 32, 146), biliary cirrhosis (Miller et al. Am. J. Gasteroenterolog. 1992, 87, 465), bowel necrosis (Sun et al.. . .

SUMM . . . to the tissue inhibitors of metalloproteinases (TIMPs). These include osteoarthritis (Woessner et al. J. Biol. Chem. 1984, 259, 3633), rheumatoid **arthritis** (Mullins et al. Biochim. Biophys. Acta 1983, 695, 117; Woolley et al. **Arthritis** Rheum. 1977, 20, 1231; Gravallese et al. **Arthritis** Rheum. 1991, 34, 1076), septic **arthritis** (Williams et al. **Arthritis** Rheum. 1990, 33, 533), tumor metastasis (Reich et al. Cancer Res. 1988, 48, 3307; Matrisian et al. Proc. Nat'l. Acad.. . .

SUMM . . . enzyme provides an approach to the treatment of the above listed diseases including osteoporosis and inflammatory disorders such as rheumatoid **arthritis** and COPD (Badger, A. M.; Bradbeer, J. N.; Votta, B.; Lee, J. C.; Adams, J. L.; Griswold, D. E. J.. . .

SUMM [0016] In rheumatoid **arthritis** (RA), the in-growth of vascular pannus may be mediated by production of angiogenic factors. Levels of immunoreactive VEGF are high. . . synovial fluid of RA patients, while VEGF levels are low in the synovial fluid of patients with other forms of **arthritis** of with degenerative joint disease (Koch et al. J. Immunol. 1994, 152, 4149). The angiogenesis inhibitor AGM-170 has been shown to prevent neovascularization of the joint in the rat collagen **arthritis** model (Peacock et al. J. Exper. Med. 1992, 175, 1135).

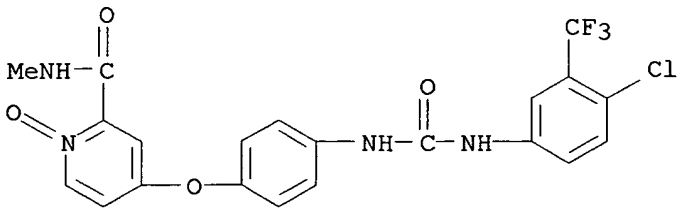
IT 284461-74-1P, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-carbamoyl(4-pyridyloxy)phenyl]urea 284462-18-6P **583840-03-3P** 583840-04-4P 583840-09-9P
(prepn. of aryl ureas for therapeutic use as kinase inhibitors)

IT 99586-65-9P, 4-Chloro-2-pyridinecarboxamide **284461-73-0P**, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)(4-pyridyloxy)phenyl]urea 284462-80-2P
(prepn. of aryl ureas for therapeutic use as kinase inhibitors)

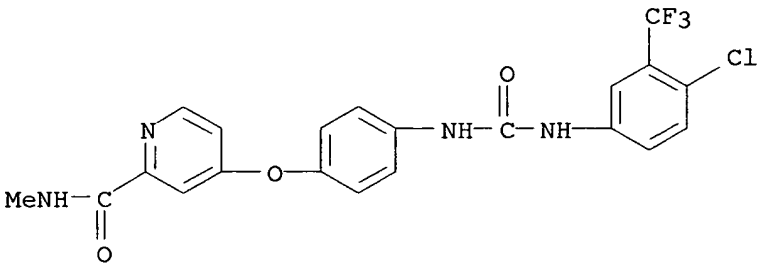
IT **583840-03-3P**
(prepn. of aryl ureas for therapeutic use as kinase inhibitors)

RN 583840-03-3 USPATFULL

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-, 1-oxide (9CI) (CA INDEX NAME)



IT **284461-73-0P**, N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-[4-[2-(N-methylcarbamoyl)(4-pyridyloxy)phenyl]urea
(prepn. of aryl ureas for therapeutic use as kinase inhibitors)
RN 284461-73-0 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L6 ANSWER 4 OF 6 USPATFULL on STN
AB This invention relates to urea compounds containing a pyridine, quinoline, or isoquinoline functionality which is oxidized at the nitrogen heteroatom and which are useful in the treatment of (i) raf mediated diseases, for example, cancer, (ii) p38 mediated diseases such as inflammation and osteoporosis, and (iii) VEGF mediated diseases such as angiogenesis disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2003:306960 USPATFULL
TITLE:	Pyridine, quinoline, and isoquinoline N-oxides as kinase inhibitors
INVENTOR(S):	Dumas, Jacques, Bethany, CT, UNITED STATES Scott, William J., Guilford, CT, UNITED STATES Riedl, Bernd, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S):	BAYER CORPORATION, Pittsburgh, PA (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003216396	A1	20031120	
APPLICATION INFO.:	US 2003-361850	A1	20030211	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2002-354935P	20020211	(60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		

DELACROIX

LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
LINE COUNT: 2076
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0007] Clinical studies have linked TNF.alpha. production and/or signaling to a number of diseases including rheumatoid **arthritis** (Maini. J. Royal Coll. Physicians London 1996, 30, 344). In addition, excessive levels of TNF.alpha. have been implicated in a. . . 1996, 149, 195), myelodysplastic syndromes (Raza et al. Int. J. Hematol. 1996, 63, 265), systemic lupus erythematosus (Maury et al. **Arthritis** Rheum. 1989, 32, 146), biliary cirrhosis (Miller et al. Am. J. Gasteroenterolog. 1992, 87, 465), bowel necrosis (Sun et al.. . .

SUMM . . . to the tissue inhibitors of metalloproteinases (TIMPs). These include osteoarthritis (Woessner et al. J. Biol. Chem. 1984, 259, 3633), rheumatoid **arthritis** (Mullins et al. Biochim. Biophys. Acta 1983, 695, 117; Woolley et al. **Arthritis** Rheum. 1977, 20, 1231; Gravallese et al. **Arthritis** Rheum. 1991, 34, 1076), septic **arthritis** (Williams et al. **Arthritis** Rheum. 1990, 33, 533), tumor metastasis (Reich et al. Cancer Res. 1988, 48, 3307; Matrisian et al. Proc. Nat'l. Acad.. . .

SUMM . . . enzyme provides an approach to the treatment of the above listed diseases including osteoporosis and inflammatory disorders such as rheumatoid **arthritis** and COPD (Badger, A. M.; Bradbeer, J. N.; Votta, B.; Lee, J. C.; Adams, J. L.; Griswold, D. E. J.. . .

SUMM [0016] In rheumatoid **arthritis** (RA), the in-growth of vascular pannus may be mediated by production of angiogenic factors. Levels of immunoreactive VEGF are high. . . synovial fluid of RA patients, while VEGF levels are low in the synovial fluid of patients with other forms of **arthritis** of with degenerative joint disease (Koch et al. J. Immunol. 1994, 152, 4149). The angiogenesis inhibitor AGM-170 has been shown to prevent neovascularization of the joint in the rat collagen **arthritis** model (Peacock et al. J. Exper. Med. 1992, 175, 1135).

SUMM . . . by p38. Accordingly, these compounds are useful therapeutic agents for such acute and chronic inflammatory and/or immunomodulatory diseases as rheumatoid **arthritis** and osteoperosis.

SUMM . . . macular degeneration; psoriasis, or bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis, rheumatoid **arthritis**, osteoarthritis, septic **arthritis**, tumor metastasis, periodontal disease, cornal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurismal aortic, birth control, dystrophobic epidermolysis bullosa, degenerative. . .

CLM What is claimed is:

. . . conditions in humans and/or other mammals: tumor growth, retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid **arthritis**, psoriasis, a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis.

. . . humans and/or other mammals: tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid **arthritis**, psoriasis, bullous disorder associated with

subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis, in combination with an infectious. . . . . ischemic retinal-vein occlusion, age related macular degeneration; psoriasis, bullous disorder associated with subepidermal blister formation, erythema multiforme, dermatitis herpetiformis, rheumatoid **arthritis**, osteoarthritis, septic **arthritis**, tumor metastasis, periodontal disease, cornal ulceration, proteinuria and coronary thrombosis from atherosclerotic plaque, aneurismal aortic, birth control, dystrophobic epidermolysis bullosa,. . .

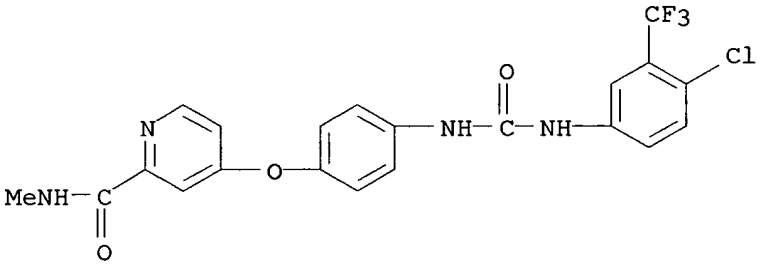
IT 123-30-8, 4-Aminophenol 320-51-4 176977-85-8, Methyl 4-chloro-2-pyridinecarboxylate hydrochloride **284461-73-0**
(prepn. of aryl ureas contg. pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors)

IT **583840-03-3P** 583840-04-4P
(prepn. of aryl ureas contg. pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors)

IT **284461-73-0**
(prepn. of aryl ureas contg. pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors)

RN 284461-73-0 USPATFULL

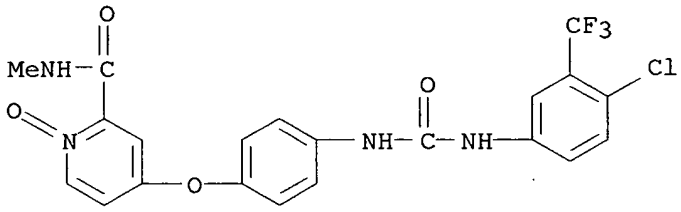
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



IT **583840-03-3P**
(prepn. of aryl ureas contg. pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors)

RN 583840-03-3 USPATFULL

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-, 1-oxide (9CI) (CA INDEX NAME)



L6 ANSWER 5 OF 6 USPATFULL on STN

AB This invention relates to methods of using aryl ureas to treat diseases mediated by the VEGF induced signal transduction pathway characterized by abnormal angiogenesis or hyperpermeability processes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:294852 USPATFULL

TITLE: Aryl ureas with angiogenisis inhibiting activity

INVENTOR(S): Dumas, Jacques, Orange, CT, UNITED STATES
Scott, William J., Guilford, CT, UNITED STATES
Elting, James, Madison, CT, UNITED STATES
Hatoum-Makdad, Holia, Hamden, CT, UNITED STATES
PATENT ASSIGNEE(S): BAYER CORPORATION, Pittsburgh, PA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003207870	A1	20031106
APPLICATION INFO.:	US 2003-361858	A1	20030211 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-354950P	20020211 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
LINE COUNT: 2356

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0009] In rheumatoid **arthritis** (RA), the in-growth of vascular pannus may be mediated by production of angiogenic factors. Levels of immunoreactive VEGF are high. . . synovial fluid of RA patients, while VEGF levels were low in the synovial fluid of patients with other forms of **arthritis** of with degenerative joint disease (Koch et al. J. Immunol. 1994, 152, 4149). The angiogenesis inhibitor AGM-170 has been shown to prevent neovascularization of the joint in the rat collagen **arthritis** model (Peacock et al. J. Exper. Med. 1992, 175, 1135).

SUMM . . . other mammals: tumor growth, retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity and age related macular degeneration; rheumatoid **arthritis**, psoriasis, or bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis, which comprises administering. . .

SUMM . . . humans and/or other mammals: tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid **arthritis**, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis in combination with another condition. . .

SUMM [0133] tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid **arthritis**, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis,

SUMM . . . treated include tumor growth, retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity and age related macular degeneration; rheumatoid **arthritis**, psoriasis, or a bullous disorder associated with subepidermal blister

formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.

SUMM . . . of the conditions above (tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid **arthritis**, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis) and another condition selected from. . .

SUMM . . . of the conditions above (tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid **arthritis**, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis) and an infectious disease selected. . .

CLM What is claimed is:

. . . conditions in humans and/or other mammals: tumor growth, retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid **arthritis**, psoriasis, a bolos disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis.

. . . conditions in humans and/or other mammals: tumor growth, retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid **arthritis**, psoriasis, a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis in combination with. . .

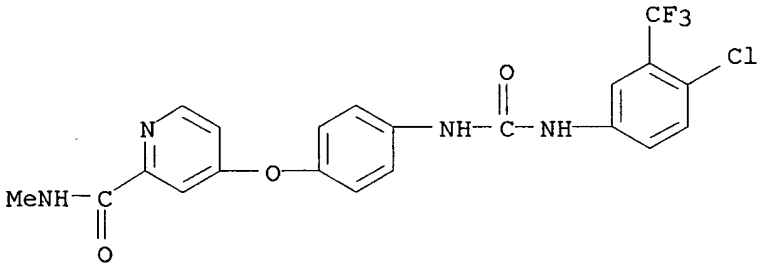
. . . humans and/or other mammals: tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid **arthritis**, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis, in combination with an infectious. . .

IT 284461-44-5P **284461-73-0P** 284461-74-1P
(prepn. of aryl ureas with angiogenesis inhibiting activity)

IT **284461-73-0P**
(prepn. of aryl ureas with angiogenesis inhibiting activity)

RN 284461-73-0 USPATFULL

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



L6 ANSWER 6 OF 6 USPATFULL on STN

AB This invention relates to the use of a group of aryl ureas in treating p38 mediated diseases, and pharmaceutical compositions for use in such

therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:153423 USPATFULL
TITLE: Omega-carboxy aryl substituted diphenyl ureas as p38 kinase inhibitors
INVENTOR(S): Riedl, Bernd, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Dumas, Jacques, Orange, CT, UNITED STATES
Khire, Uday, Handen, CT, UNITED STATES
Lowinger, Timothy B., Nishinomiya, JAPAN
William, Scott J., Guilford, CT, UNITED STATES
Smith, Roger A., Madison, CT, UNITED STATES
Wood, Jill E., Hamden, CT, UNITED STATES
Monahan, Mary-Katherine, Hamden, CT, UNITED STATES
Naero, Reina, Hamden, CT, UNITED STATES
Renick, Joel, Milford, CT, UNITED STATES
Sibley, Robert N., North Haven, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003105091	A1	20030605
APPLICATION INFO.:	US 2002-86417	A1	20020304 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-425229, filed on 22 Oct 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-257265, filed on 25 Feb 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115878P	19990113 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
LINE COUNT: 4076

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0003] Two classes of effector molecules which are critical for the progression of rheumatoid **arthritis** are pro-inflammatory cytokines and tissue degrading proteases. Recently, a family of kinases was described which is instrumental in controlling the. . .

SUMM [0006] Clinical studies have linked TNF.alpha. production and/or signaling to a number of diseases including rheumatoid **arthritis** (Maini. J. Royal Coll. Physicians London 1996, 30, 344). In addition, excessive levels of TNF.alpha. have been implicated in a. . . 1996, 149, 195), myelodysplastic syndromes (Raza et al. Int. J. Hematol. 1996, 63, 265), systemic lupus erythematosus (Maury et al. **Arthritis** Rheum. 1989, 32, 146), biliary cirrhosis (Miller et al. Am. J. Gasteroenterolog. 1992, 87, 465), bowel necrosis (Sun et al.. . .

SUMM . . . to the tissue inhibitors of metalloproteinases (TIMPs). These include osteoarthritis (Woessner et al. J. Biol. Chem. 1984, 259, 3633), rheumatoid **arthritis** (Mullins et al. Biochim. Biophys. Acta 1983, 695, 117; Woolley et al. **Arthritis** Rheum. 1977, 20, 1231; Gravallese et al. **Arthritis** Rheum. 1991, 34, 1076), septic **arthritis** (Williams et al. **Arthritis** Rheum. 1990, 33, 533), tumor metastasis (Reich et al. Cancer Res. 1988, 48, 3307; Matrisian et al. Proc. Nat'l. Acad.. . .

SUMM . . . edema in the rat paw, arachadonic acid-induced peritonitis in the mouse, fetal rat long bone resorption, murine type II collagen-induced **arthritis**, and Fruend's adjuvant-induced **arthritis** in the rat. Thus, inhibitors of p38 will be useful in treating diseases mediated by one or more of the. . .

SUMM [0011] The need for new therapies is especially important in the case of **arthritic** diseases. The primary disabling effect of osteoarthritis, rheumatoid **arthritis** and septic **arthritis** is the progressive loss of articular cartilage and thereby normal joint function. No marketed pharmaceutical agent is able to prevent. . .

SUMM [0014] Accordingly, these compounds are useful therapeutic agents for such acute and chronic inflammatory and/or immunomodulatory diseases as rheumatoid **arthritis**, osteoarthritis, septic **arthritis**, rheumatic fever, bone resorption, postmenopausal osteoperosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response. . .

CLM What is claimed is:

. . . as in claim 1 wherein the condition within a host treated by administering a compound of formula I is rheumatoid **arthritis**, osteoarthritis, septic **arthritis**, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophobic epidermolysis bullosa, degenerative. . .

IT 228418-48-2P 284461-33-2P 284461-34-3P 284461-35-4P 284461-36-5P
284461-37-6P 284461-38-7P 284461-39-8P 284461-40-1P 284461-41-2P
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284461-67-2P 284461-68-3P 284461-69-4P 284461-70-7P 284461-71-8P
284461-72-9P **284461-73-0P** 284461-74-1P 284461-75-2P
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284461-97-8P 284461-98-9P 284461-99-0P 284462-00-6P 284462-01-7P
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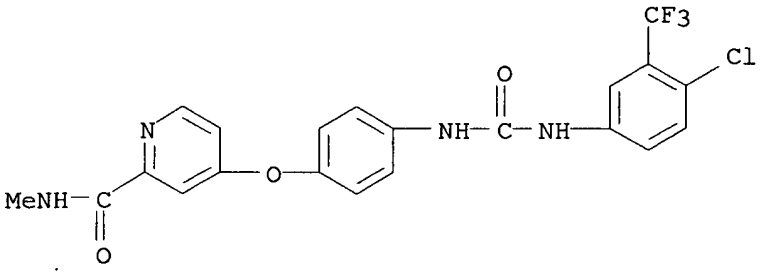
284462-28-8P 284462-29-9P 284462-30-2P
284462-31-3P 284462-32-4P 284462-33-5P 284462-34-6P 284462-35-7P
284462-36-8P 284462-70-0P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

IT **284461-73-0P 284461-78-5P 284461-80-9P**
284461-83-2P 284462-28-8P 284462-29-9P
284462-30-2P
(prepn. of .omega.-carboxy aryl substituted di-Ph ureas as p38 kinase inhibitors)

RN 284461-73-0 USPATFULL

CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284461-78-5 USPATFULL
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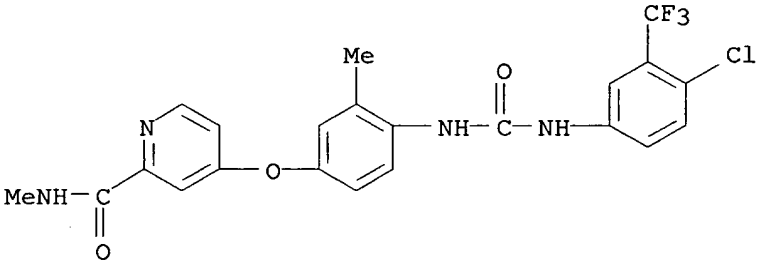
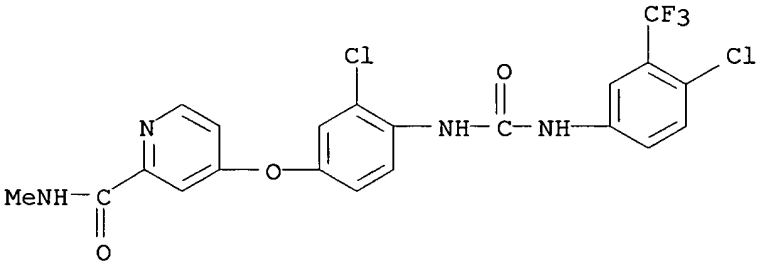
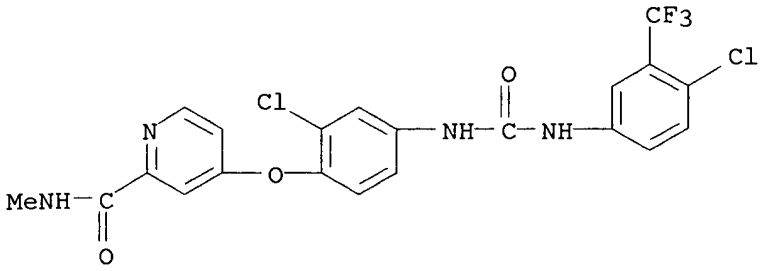


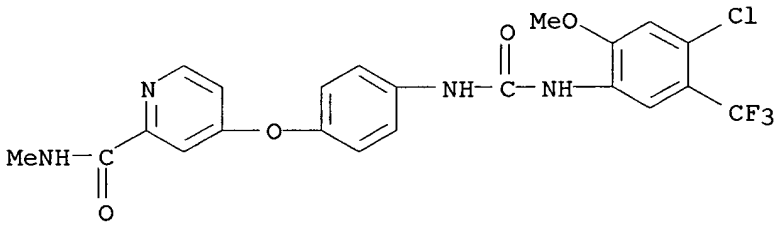
RN 284461-80-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



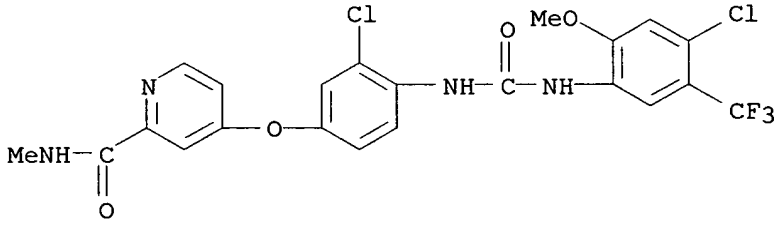
RN 284461-83-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



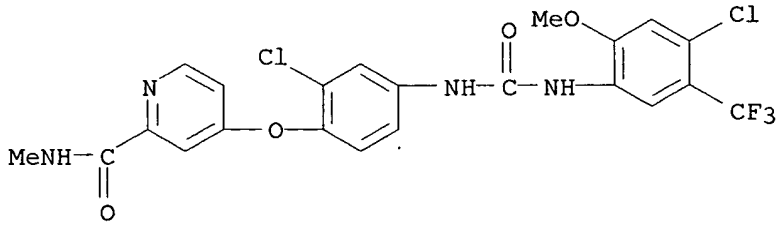
RN 284462-28-8 USPATFULL
CN 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



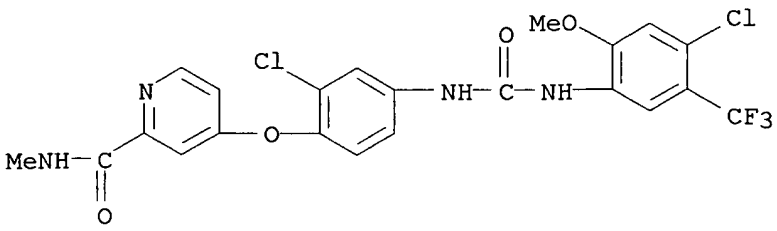
RN 284462-29-9 USPATFULL
CN 2-Pyridinecarboxamide, 4-[3-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



RN 284462-30-2 USPATFULL
CN 2-Pyridinecarboxamide, 4-[2-chloro-4-[[[[4-chloro-2-methoxy-5-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl- (9CI) (CA INDEX NAME)



DELACROIX


MeO
Cl
O
Cl
NH
C
NH
N
CF3
O
MeNH
C
O

FILE 'HCAPLUS' ENTERED AT 21:13:28 ON 22 JAN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'USPATFULL' ENTERED AT 21:13:28 ON 22 JAN 2004

elected species

=> s l7 not l9
L10 5 L7 NOT L9

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11 5 DUP REM L10 (0 DUPLICATES REMOVED)

=> d l11 ibib 1-5

L11 ANSWER 1 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2003:294854 USPATFULL
TITLE: OMEGA-CARBOXYARYL SUBSTITUTED DIPHENYL UREAS AS RAF KINASE INHIBITORS
INVENTOR(S): Riedl, Bernd, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Dumas, Jacques, Orange, CT, UNITED STATES
Khire, Uday, Hamden, CT, UNITED STATES
Lowinger, Timothy B., Nishinomiya City, JAPAN
Scott, William J., Guilford, CT, UNITED STATES
Smith, Roger A., Madison, CT, UNITED STATES
Wood, Jill E., Hamden, CT, UNITED STATES
Monahan, Mary-Katherine, Hamden, CT, UNITED STATES
Natero, Reina, Hamden, CT, UNITED STATES
Renick, Joel, Milford, CT, UNITED STATES
Sibley, Robert N., North Haven, CT, UNITED STATES
PATENT ASSIGNEE(S): BAYER CORPORATION, Pittsburgh, PA (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003207872	A1	20031106	
APPLICATION INFO.:	US 2002-42226	A1	20020111	(10)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS: 67
EXEMPLARY CLAIM: 1
LINE COUNT: 3713
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 2 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2003:258389 USPATFULL
TITLE: omega-carboxyaryl substituted diphenyl ureas as raf kinase inhibitors
INVENTOR(S): Riedl, Bernd, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Dumas, Jacques, Orange, CT, UNITED STATES
Khire, Uday, Hamden, CT, UNITED STATES
Lowinger, Timothy B., Nishinomiya City, JAPAN

Scott, William J., Guilford, CT, UNITED STATES
Smith, Roger A., Madison, CT, UNITED STATES
Wood, Jill E., North Haven, CT, UNITED STATES
Monahan, Mary-Katherine, Hamden, CT, UNITED STATES
Natero, Reina, Hamden, CT, UNITED STATES
Renick, Joel, San Diego, CA, UNITED STATES
Sibley, Robert N., North Haven, CT, UNITED STATES
PATENT ASSIGNEE(S): BAYER CORPORATION, Piittsburgh, PA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003181442	A1	20030925
APPLICATION INFO.:	US 2001-993647	A1	20011127 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS: 67
EXEMPLARY CLAIM: 1
LINE COUNT: 3729
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 3 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2003:207917 USPATFULL
TITLE: Omega-carboxyaryl substituted diphenyl ureas as raf kinase inhibitors
INVENTOR(S): Riedl, Bernd, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Dumas, Jacques, Orange, CT, UNITED STATES
Khire, Uday, Hamden, CT, UNITED STATES
Lowinger, Timothy B., Nishinomiya City, JAPAN
Scott, William J., Guilford, CT, UNITED STATES
Smith, Roger A., Madison, CT, UNITED STATES
Wood, Jill E., Hamden, CT, UNITED STATES
Monahan, Mary-Katherine, Hamden, CT, UNITED STATES
Natero, Reina, Hamden, CT, UNITED STATES
Renick, Joel, Milford, CT, UNITED STATES
Sibley, Robert N., North Haven, CT, UNITED STATES
PATENT ASSIGNEE(S): BAYER CORPORATION, Pittsburgh, PA, 15205 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003144278	A1	20030731
APPLICATION INFO.:	US 2002-283248	A1	20021030 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-42203, filed on 11 Jan 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-367380P	20010112 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS: 67
EXEMPLARY CLAIM: 1

LINE COUNT: 3733
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 4 OF 5 USPATFULL on STN
ACCESSION NUMBER: 2002:295343 USPATFULL
TITLE: Inhibition of RAF kinase using quinolyl, isoquinolyl or pyridyl ureas
INVENTOR(S): Dumas, Jacques, Orange, CT, UNITED STATES
Riedl, Bernd, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Khire, Uday, Hamden, CT, UNITED STATES
Wood, Jill E., Hamden, CT, UNITED STATES
Robert, Sibley N., North Haven, CT, UNITED STATES
Monahan, Mary-Katherine, Hamden, CT, UNITED STATES
Renick, Joel, Milford, CT, UNITED STATES
Gunn, David E., Hamden, CT, UNITED STATES
Lowinger, Timothy B., Nishinomiya City, JAPAN
Scott, William J., Guilford, CT, UNITED STATES
Smith, Roger A., Madison, CT, UNITED STATES
PATENT ASSIGNEE(S): BAYER CORPORATION (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002165394	A1	20021107
APPLICATION INFO.:	US 2001-777920	A1	20010207 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-758548, filed on 12 Jan 2001, PENDING Continuation-in-part of Ser. No. US 1999-425228, filed on 22 Oct 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-257266, filed on 25 Feb 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115877P	19990113 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
LINE COUNT: 3722
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:493376 HCAPLUS
DOCUMENT NUMBER: 133:120155
TITLE: Preparation of .omega.-carboxy aryl substituted diphenyl ureas as p38 kinase inhibitors
INVENTOR(S): Riedl, Bernd; Dumas, Jacques; Khire, Uday; Lowinger, Timothy B.; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Monahan, Mary-Katherine; Natero, Reina; Renick, Joel; Sibley, Robert N.
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000041698	A1	20000720	WO 2000-US768	20000113
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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EP 1158985	A1	20011205	EP 2000-905597	20000113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2003139605	A1	20030724	US 2002-71248	20020211
US 2003105091	A1	20030605	US 2002-86417	20020304

PRIORITY APPLN. INFO.:	US 1999-115878P	P	19990113
	US 1999-257265	A2	19990225
	US 1999-425229	A2	19991022
	US 1999-115877P	P	19990113
	US 1999-257266	B2	19990225
	US 1999-425228	B1	19991022
	WO 2000-US768	W	20000113
	US 2001-948915	A1	20010910

OTHER SOURCE(S): MARPAT 133:120155

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT